The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease

Dretzke, Janine; Riley, Richard D; Lordkipanidzé, Marie; Jowett, Sue; O'Donnell, Jennifer; Ensor, Joie; Moloney, Eoin; Price, Malcolm; Raichand, Smriti; Hodgkinson, James; Bayliss, Susan; Fitzmaurice, David; Moore, David

DOI:
10.3310/hta19370

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Dretzke, J, Riley, RD, Lordkipanidzé, M, Jowett, S, O'Donnell, J, Ensor, J, Moloney, E, Price, M, Raichand, S, Hodgkinson, J, Bayliss, S, Fitzmaurice, D & Moore, D 2015, 'The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: A systematic review and economic evaluation', *Health Technology Assessment*, vol. 19, no. 37, pp. 1-366. https://doi.org/10.3310/hta19370

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 19 ISSUE 37 MAY 2015
ISSN 1366-5278

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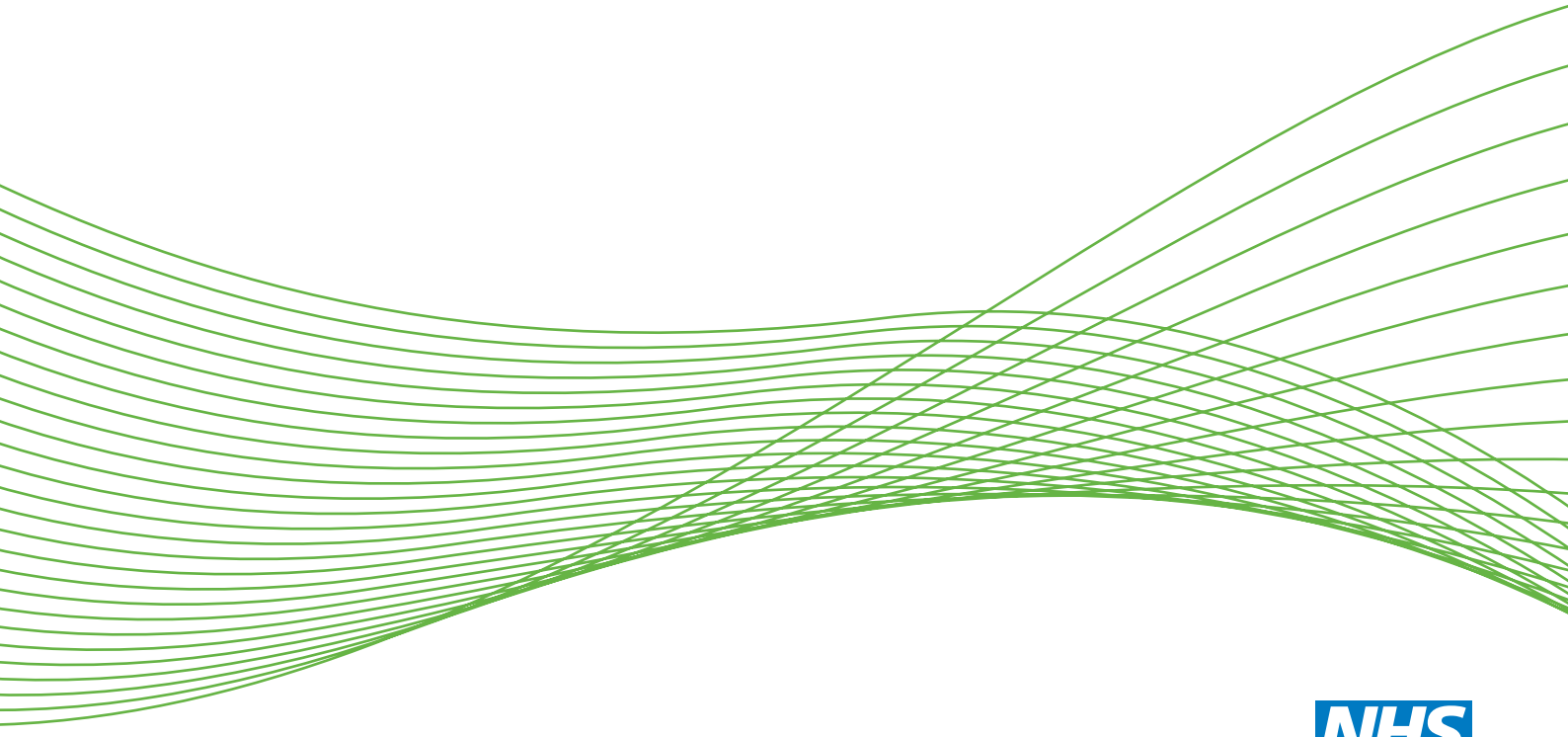

NHS
National Institute for Health Research

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Declared competing interests of authors: Marie Lordkipanidzé has received speaker honoraria from Eli Lilly, which manufactures the antiplatelet agent prasugrel. David Fitzmaurice has received honoraria from Boehringer Ingelheim, Sanofi-aventis and AstraZeneca, but not in relation to antiplatelet therapy. All other authors declare no competing interests.

Published May 2015
DOI: 10.3310/hta19370

This report should be referenced as follows:

Dretzke J, Riley RD, Lordkipanidzé M, Jowett S, O'Donnell J, Ensor J, *et al*. The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: a systematic review and economic evaluation. *Health Technol Assess* 2015;**19**(37).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/36/02. The contractual start date was in December 2011. The draft report began editorial review in June 2013 and was accepted for publication in March 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: a systematic review and economic evaluation

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Background: The use of aspirin is well established for secondary prevention of cardiovascular disease. However, a proportion of patients suffer repeat cardiovascular events despite being prescribed aspirin treatment. It is uncertain whether or not this is due to an inherent inability of aspirin to sufficiently modify platelet activity. This report aims to investigate whether or not insufficient platelet function inhibition by aspirin ('aspirin resistance'), as defined using platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes, and further, whether or not patients at risk of future adverse clinical events can be identified through PFTs.

Objectives: To review systematically the clinical effectiveness and cost-effectiveness evidence regarding the association between PFT designation of 'aspirin resistance' and the risk of adverse clinical outcome(s) in patients prescribed aspirin therapy. To undertake exploratory model-based cost-effectiveness analysis on the use of PFTs.

Data sources: Bibliographic databases (e.g. MEDLINE from inception and EMBASE from 1980), conference proceedings and ongoing trial registries up to April 2012.

Methods: Standard systematic review methods were used for identifying clinical and cost studies. A risk-of-bias assessment tool was adapted from checklists for prognostic and diagnostic studies. (Un)adjusted odds and hazard ratios for the association between 'aspirin resistance', for different PFTs, and clinical outcomes are presented; however, heterogeneity between studies precluded pooling of results. A speculative economic model of a PFT and change of therapy strategy was developed.

Results: One hundred and eight relevant studies using a variety of PFTs, 58 in patients on aspirin monotherapy, were analysed in detail. Results indicated that some PFTs may have some prognostic utility, i.e. a trend for more clinical events to be associated with groups classified as 'aspirin resistant'. Methodological and clinical heterogeneity prevented a quantitative summary of prognostic effect. Study-level effect sizes were generally small and absolute outcome risk was not substantially different between 'aspirin resistant' and 'aspirin sensitive' designations.

No studies on the cost-effectiveness of PFTs for 'aspirin resistance' were identified. Based on assumptions of PFTs being able to accurately identify patients at high risk of clinical events and such patients benefiting from treatment modification, the economic model found that a test–treat strategy was likely to be cost-effective. However, neither assumption is currently evidence based.

Limitations: Poor or incomplete reporting of studies suggests a potentially large volume of inaccessible data. Analyses were confined to studies on patients prescribed aspirin as sole antiplatelet therapy at the time of PFT. Clinical and methodological heterogeneity across studies precluded meta-analysis. Given the lack of robust data the economic modelling was speculative.

Conclusions: Although evidence indicates that some PFTs may have some prognostic value, methodological and clinical heterogeneity between studies and different approaches to analyses create confusion and inconsistency in prognostic results, and prevented a quantitative summary of their prognostic effect. Protocol-driven and adequately powered primary studies are needed, using standardised methods of measurements to evaluate the prognostic ability of each test in the same population(s), and ideally presenting individual patient data. For any PFT to inform individual risk prediction, it will likely need to be considered in combination with other prognostic factors, within a prognostic model.

Study registration: This study is registered as PROSPERO 2012:CRD42012002151.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

'**Aspirin resistant**' Those individuals prescribed aspirin therapy classified as having insufficient inhibition of platelet reactivity (i.e. elevated platelet reactivity) based on the platelet function test and threshold specified by the authors of the relevant studies.

'**Aspirin sensitive**' Those individuals prescribed aspirin therapy classified as having sufficient inhibition of platelet reactivity (i.e. low platelet reactivity) based on the platelet function test and threshold specified by the authors of the relevant studies.

Major adverse cardiac event (MACE) Individual definitions vary between studies, but for the purposes of this report, this is any composite measure including death and cardiovascular events with or without ischaemic events.

Predictive utility Whether or not a platelet function test with good prognostic utility is able for individual patients to distinguish between those who will and those who will not have an adverse outcome, in order to determine if treatment modification should be considered based on the test result.

Prognostic utility Whether or not a platelet function test is able to distinguish between groups of patients with different average outcome risks even if it does not accurately predict individual outcome risk.

List of abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AMSTAR	Assessment of Multiple Systematic Reviews
ARU	aspirin reaction unit
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEPI	collagen/epinephrine
CI	confidence interval
COX	cyclo-oxygenase
CVD	cerebrovascular disease
ET	essential thrombocythaemia
GI	gastrointestinal
GP	general practitioner
HR	hazard ratio
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
IPD	individual patient data
LEAD	lower-extremity artery disease
LTA	light transmission aggregometry
MACE	major adverse cardiac event
MI	myocardial infarction
NHS EED	NHS Economic Evaluation Database
NIHR	National Institute for Health Research
NIHSS	National Institutes of Health Stroke Scale
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PFA-100®	platelet function analyser-100
PFT	platelet function test
PPCI	primary percutaneous coronary intervention
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
ROC	receiver operating characteristic
RR	rate ratio
SD	standard deviation
SVG	saphenous vein graft
TEG	thromboelastography
TIA	transient ischaemic attack
TxA_2	thromboxane A_2
TxB_2	thromboxane B_2
UA	unstable angina
WBA	whole-blood aggregometry

Plain English summary

Aspirin is prescribed for people who have had diseases of the heart or circulation, such as a heart attack, angina (chest pain) or stroke. Aspirin is thought to lower the risk of further disease by preventing platelets (a type of blood cell) from sticking together and forming blood clots. In some people aspirin does not seem to work as well as expected, and further heart attacks, strokes or other events are more common. Platelet function tests (PFTs) are a type of test that can assess how platelets are aggregating ('sticking' together) and whether or not taking aspirin reduces the aggregation. Depending on the amount of platelet aggregation, a person may be classified as 'aspirin resistant', meaning that their platelet aggregation might not be reduced sufficiently by aspirin.

The aim of this report was to gather all the studies that have looked at the relationship between platelet aggregation (assessed using a PFT) and the risk of having a cardiovascular event, and to see if 'aspirin resistance' is associated with an increased chance of future heart attacks or strokes. If patients at higher risk could be identified, then a change in their treatment might be considered to prevent future problems.

Fifty-eight studies were reviewed in detail and these indicate that, on average, some tests may have some value, but differences between the studies create a confused and inconsistent picture. As such, no firm conclusions about the value of specific PFTs for individual patients could be made. Therefore, this report makes recommendations for future research.

Scientific summary

Background

Aspirin is recommended in cardiovascular disease to prevent future thrombotic complications. However, not all patients benefit from being prescribed aspirin to the same extent, and the question is therefore whether or not patients who suffer events do so because of insufficient antiplatelet effect of aspirin. This systematic review assesses whether or not insufficient platelet function inhibition by aspirin, as measured by platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes. This process was undertaken in order to ascertain the prognostic utility of the available PFTs. For the purposes of this report, those individuals prescribed aspirin and classified as having insufficient inhibition of platelet reactivity (i.e. elevated platelet reactivity), based on a PFT and threshold specified by the authors of the studies, are deemed to be 'aspirin resistant'.

Objectives

1. To review systematically the clinical evidence relating platelet function test results to the risk of adverse clinical outcome(s) in patients on aspirin therapy with established cardiovascular disease, cerebrovascular disease (CVD) or diabetes. More specifically, to determine whether or not PFT results have any utility as a prognostic factor and, should that be demonstrated, whether or not they also have any utility in identifying (diagnosing) individuals at higher risk of cardiovascular events.
2. To review systematically the evidence relating to the economic utility of PFTs in patients on aspirin therapy with established cardiovascular disease, CVD, or diabetes.
3. To undertake exploratory model-based cost-effectiveness analysis of the use of PFTs in patients on long-term aspirin therapy with investigation of the potential for populating the model with data based on the results of the systematic review outlined in objective 1.

Methods

For the systematic reviews standard methods were employed.

For the review of prognostic utility, studies were eligible for inclusion if they were prospective primary studies or systematic reviews of studies assessing PFTs in relation to clinical outcomes; were in patients aged $\geq$ 18 years on aspirin, with established cardiovascular disease, CVD, or diabetes; and included either a cyclo-oxygenase-1 enzyme-specific PFT (which measures aspirin response specifically) or a global PFT in patients receiving aspirin as the only antiplatelet therapy. Relevant clinical outcomes were vascular events, haemorrhagic events, all-cause mortality, mortality due to vascular events and composite outcomes containing the above [e.g. major adverse cardiac events (MACEs)]. Reported outcomes had to occur after the undertaking of a PFT and the post-test follow-up period had to be 7 days or longer.

Bibliographic databases (e.g. MEDLINE from inception and EMBASE from 1980, and ongoing studies and conference proceedings databases) were searched up to April 2012, and citation searching was undertaken. Study selection was performed in duplicate using predefined criteria, with recourse to full texts where necessary, and disagreements were resolved by discussion or by referral to a third reviewer. No language or publication restrictions were placed on searches or study selection.

Risk of bias was assessed by one reviewer and independently checked by a second. Disagreements were resolved by discussion. Assessment criteria were based on criteria for checking the quality of prognostic studies and the quality assessment of diagnostic accuracy studies (revised tool) (QUADAS-2). Criteria related to the domains of patient selection, PFT, outcomes, study attrition and confounding.

Data extraction was conducted by one reviewer using a standardised, piloted data extraction form, and independently checked by a second. Disagreements were resolved through discussion or referral to a third reviewer. Data were extracted on study design and characteristics, patient characteristics, antiplatelet regimens, PFT utilised, outcome measures and length of follow-up, data required for analyses, statistical methods employed and their appropriateness.

Studies were grouped according to whether patients were prescribed monotherapy (aspirin only) or dual therapy (with a second antiplatelet agent added to aspirin) at the time of PFTs in order to distinguish between patients with different therapeutic needs. It was decided to undertake a stepwise approach to reporting and analysing studies, starting with monotherapy studies and then moving on to dual-therapy studies owing to the added complexity engendered in the latter. As prognostic utility of PFTs in patients treated with aspirin as monotherapy was not convincingly demonstrated, it was decided not to undertake analyses of the dual-therapy studies. However, all data extracted in relation to dual-therapy studies have been made available to readers via a web portal.

Where possible, results were presented for different PFTs, different outcome measures (e.g. death, MACE) and different outcome statistics (e.g. odds ratios, hazard ratios). Adjusted and unadjusted results were also presented separately. Where more than one threshold was used (for classification of 'aspirin resistance'), results were presented for all thresholds. Methodological and clinical heterogeneity precluded pooling of results, but forest plots were used to visualise data and indicate heterogeneity between studies.

Similar review methods were employed for the review of cost-effectiveness studies. Any of the following study designs was eligible: cost–consequence analysis, cost-effectiveness analysis, cost–benefit analysis, cost–utility analysis and cost studies. Outcomes of interest were cost-effectiveness, cost estimates, utilisation estimates and quality-of-life estimates.

A speculative economic model developed as a decision tree combined with a Markov model was built to estimate the cost-effectiveness of PFTs, with the option of change in treatment based on a designation of 'aspirin resistant' compared with no testing and no change in treatment (current treatment), from a NHS and Personal Social Services perspective.

Results and discussion

Systematic review of the primary studies linking platelet function testing and future thrombotic risk

Searches identified 120 articles reporting the result(s) of one or more PFTs in relation to clinical outcome data, and these articles represented 108 separate studies. Fifty-eight studies reported on a patient group solely or predominantly receiving aspirin as monotherapy at the time of testing. The PFTs used in these studies were (i) light transmission aggregometry (LTA), (ii) VerifyNow® Aspirin (Accumetrics, Inc., San Diego, CA, USA), (iii) measurement of urinary or serum/plasma thromboxane B_2 metabolites, (iv) platelet function analyser-100 (PFA-100®; Siemens, Malvern, PA, USA), (v) whole-blood aggregometry (WBA), (vi) thromboelastography (TEG) and (vii) other miscellaneous tests.

The studies were highly heterogeneous with regard to patient groups studied, designation of 'aspirin resistance', range and definition of clinical outcomes and types of statistics reported.

Nineteen studies used LTA, mainly in stable coronary artery disease populations. The most frequently reported test threshold to define 'aspirin resistance' was 20% platelet aggregation induced by arachidonic acid, although other agonists (particularly adenosine diphosphate and collagen) were also used with different threshold levels. For the point-of-care VerifyNow® Aspirin assay, seven studies were identified. The most common threshold used to define poor response to aspirin was 550 aspirin response units, as recommended by the manufacturer. Eleven studies were identified using thromboxane metabolites to define 'aspirin resistance'. Thromboxane metabolites were measured in urine, serum or plasma, usually by enzyme immunoassay, although radioactive labelling was also reported. Methods for deriving thresholds and thresholds to define 'aspirin resistance' themselves were variable. For the PFA-100® assay, 21 studies were identified, for the most part in stable populations, although studies in acute populations contributed substantially to results. The collagen/epinephrine cartridge was used to assess platelet responses to aspirin. For WBA, eight studies were identified, all in stable disease patients except in one study. The most commonly reported agonist was arachidonic acid, although collagen was also sometimes used. The threshold to define 'aspirin resistance' was not always reported or consistent across studies. The TEG system was reported in three studies (two with a stable, one with an acute disease population), and a threshold for 'aspirin resistance' of 50% was consistently used across studies.

In general, study reporting lacked detail to assess quality criteria, regardless of the PFT used, thus hampering an overall risk-of-bias assessment. Lack of detail related in particular to blinding (to patient characteristics or of outcome assessors), loss-to-follow-up information and level of compliance with aspirin treatment. There was no consistent reporting of adjusted analyses.

Overall, there is a possible trend suggestive of more clinical events occurring in those groups of patients designated 'aspirin resistant', with some results in some studies showing statistical significance; this is the case across the majority of tests (LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement), though to a lesser extent for TEG, and with data for WBA not allowing many conclusions to be drawn. This trend is also fairly consistent across some outcomes (i.e. death, MACEs and ischaemic/thrombotic events) irrespective of test, though the direction of effect is not always consistent for different thresholds applied to the data from the same study. There are very limited data on bleeding events and thus no inference could be drawn.

The results suggest that PFTs (specifically LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement and TEG) may have some prognostic value as they are fairly consistently associated with elevated risk of cardiovascular events (MACE or death). However, as meta-analysis was not possible, no firm quantitative conclusions can be drawn as to the prognostic value. Given that the effect sizes for an association with clinical events are relatively small and highly uncertain, a determination of the diagnostic utility of PFTs (for determining if an individual is at higher risk of a clinical event) was not possible in this report.

Review of the existing systematic reviews

Fifteen systematic reviews relevant to prognostic utility were identified, and of these, four were considered methodologically more robust than the others. All four reviews found a positive association between aspirin non-responder status ('resistance') and likelihood of adverse cardiovascular outcomes, despite their differences in precise research question, range of included studies and primary outcome measures. However, these reviews had important deficiencies, variously:

- a lack of a rigorous and transparent approach to quality assessment
- insufficient comprehensiveness and a failure to account for the complexity of the field by not considering the effect of different PFTs, thresholds, etc.
- not distinguishing between adjusted and non-adjusted statistical data
- uncertainty regarding whether or not patients receiving aspirin as monotherapy and participants who received additional antiplatelet agents (most commonly dual antiplatelet therapy with aspirin and clopidogrel) were combined in the analysis

- uncertainty over whether included studies were prospective or retrospective in design
- failure to account for the effect of non-compliance.

In this context, caution must be exercised in interpretation of the findings from these previous reviews.

Systematic review of economic evaluations and economic model

Currently, there is no existing economic evidence on the cost or cost-effectiveness of platelet function testing for 'aspirin resistance'. This report presents the first model to attempt to estimate the cost-effectiveness of a 'test and change treatment' strategy using platelet function testing to define an at-risk population. The model (based on a decision tree coupled with a Markov model) is highly speculative owing to the large degree of heterogeneity and uncertainty around the prognostic utility of PFTs, and it contains numerous assumptions. This has been addressed, where possible, by deterministic sensitivity analysis and also by taking into account the uncertainty around many of the model parameter values. In addition, further analyses have been presented to show scenarios where platelet function testing for 'aspirin resistance' and a change in treatment would not be cost-effective.

Assuming a PFT can accurately identify patients at higher risk of adverse clinical outcomes while receiving aspirin therapy as the sole antiplatelet agent and patients changed to an effective treatment, a 'test and change treatment' option is very likely to be cost-effective. Conversely, if a PFT cannot identify these patients, and a treatment change is not effective in reducing adverse clinical outcome (MACE) risk, then a 'test and change treatment' strategy is not cost-effective. The parameters with the greatest impact on model results are the proportion that are correctly identified as having a high risk of clinical outcome, the effectiveness of a change in treatment if designated 'aspirin resistant', the cost of a test and the cost of a change in treatment. The accuracy of testing, the additional risk of an adverse outcome associated with a designation of 'aspirin resistant' and the effectiveness of a change in therapy are the most uncertain. The model requires more robust data on all of these aspects.

Conclusions

The current report has demonstrated a lack of a consistent association between a laboratory designation of 'aspirin resistance' and clinical outcome, on any test and in any outcome, despite the existence of a vast number of studies which have sought to clarify this association. Although evidence indicates that some tests may have some prognostic value, methodological and clinical heterogeneity between studies and different approaches to analyses create confusion and inconsistency in prognostic results, and prevented a quantitative summary of their prognostic effect. As no large/consistent effect for prognostic utility could be shown, consideration of diagnostic utility was not meaningful.

Recommendations for future research

There is a need for large, protocol-driven and adequately powered primary studies using standardised and agreed methods of measurement to evaluate the prognostic ability of each test in the same population(s). For the tests to inform individual risk prediction, it is likely that they need to be considered in combination and alongside other prognostic factors, within a prognostic model. Once these issues have been addressed it may be possible to undertake a 'test–treat trial' using a prognostic model to tailor antiplatelet therapy to individuals.

Study registration

This study is registered as PROSPERO 2012:CRD42012002151.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Cardiovascular disease is the leading cause of death in the developed world, with coronary artery disease (CAD) and stroke accounting for one-quarter of all deaths in the UK.[1] Important progress has been made in the management of heart disease over the last century, driving the incidence of disease down in both men and women. Among the many beneficial medical therapies which have been shown to decrease the risk of recurrent vascular events, antiplatelet agents have become the cornerstone of therapy in patients suffering from atherosclerotic vascular disease. It is thus not surprising that over 40,000 tons of aspirin are produced every year worldwide, and 35,000 kg of aspirin are consumed every day in the USA alone (the figure for the UK is 6000 kg per day).[2] In the UK, aspirin was the second most prescribed drug in 2011, with 32.4 million prescriptions dispensed in the community, 95% of which were for cardioprotection.[3]

Indications for antiplatelet therapy

The use of antiplatelet agents covers a large spectrum of vascular diseases.[4] In primary prevention, antiplatelet agents can be given to patients at high risk of thrombotic events, such as patients with multiple risk factors for CAD or diabetes.[5] In secondary prevention, antiplatelet agents can be given either acutely in patients with acute coronary syndromes (ACSs), following percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), or chronically in patients with stable CAD, in patients with a history of transient ischaemic attacks (TIAs) or strokes and patients with peripheral arterial disease (PAD).[5] The benefit of aspirin therapy in each of these pathologies is related to the underlying thrombotic risk, and is usually greatest in high-risk individuals and lowest in individuals with no overt atherosclerotic disease (*Figure 1*).

Antiplatelet therapy in primary prevention of cardiovascular disease

There is little clinical evidence to support the use of antiplatelets for the primary prevention of cardiovascular events in patients with a cardiovascular disease risk less than 20%.[4] In patient groups carrying the highest cardiovascular disease risk, the benefit (i.e. the expected number of individuals avoiding a serious vascular event by using aspirin) exceeds the risk associated with aspirin treatment (i.e. experiencing a major bleed).[5] The latest meta-analysis by the Antithrombotic Trialists' Collaboration found that aspirin therapy in primary prevention of cardiovascular events resulted in a 12% proportional reduction in the incidence of serious vascular events [rate ratio (RR) 0.88, 95% confidence interval (CI) 0.82 to 0.94] and an 18% proportional reduction in the incidence of major coronary events (RR 0.82, 95% CI 0.75 to 0.90).[4] On the other hand, aspirin was associated with an increase in major gastrointestinal

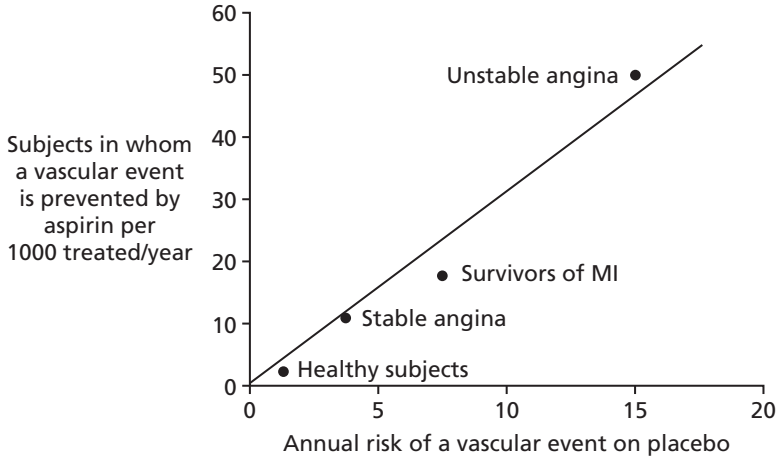

FIGURE 1 The benefit of aspirin in terms of risk prevention in different patient groups. From Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**(2 Suppl.): e89–119.[5] Reproduced with permission from the American College of Chest Physicians. MI, myocardial infarction.

(GI) and other extracranial bleeds (RR 1.54, 95% CI 1.30 to 1.82). In absolute numbers, however, the decrease in major coronary events from 0.34% to 0.28% per year is only slightly superior to the increase in bleeding events from 0.07% to 0.10% per year.[4] As a consequence, most guidelines advise against daily aspirin therapy in men and women without evidence of manifest vascular disease. However, daily aspirin therapy (75–160 mg) can be considered in apparently healthy individuals in whom the vascular risk is considered high and the bleeding risk low.[5,6]

Within the primary prevention populations, patients suffering from diabetes mellitus have specific guidelines when it comes to antiplatelet therapy in prevention of vascular events.[7] This stems from epidemiological studies which have shown that diabetic patients have a two- to three-fold increase in risk of major ischaemic events. Despite the higher risk of cardiovascular disease, the benefit of giving aspirin in patients suffering from diabetes alone is, however, less certain.[8] Recent guidelines reflect this by moving away from a universal recommendation for aspirin in all diabetic patients, and advising daily aspirin therapy only in diabetic patients with concomitant risk factors for CAD where the most benefit can be gained.[7,8] As a consequence, daily administration of aspirin is usually initiated in primary prevention in diabetic patients at increased cardiovascular risk (10-year risk > 10%). This includes most men aged > 50 years or women aged > 60 years who have at least one additional major risk factor (family history of cardiovascular disease, hypertension, smoking, dyslipidaemia or albuminuria).[7]

Antiplatelet therapy in secondary prevention of cardiovascular disease

Daily low-dose aspirin therapy (75–325 mg) is strongly recommended for all patients with established cardiovascular disease. In patients with a prior cardiovascular event, evidence that daily aspirin therapy reduces the risk of major adverse cardiovascular events is arguably strong.[4] Although the proportional reduction in risk of any serious vascular event does not differ significantly between primary and secondary prevention trials, the absolute risk reduction is much greater in secondary prevention, thus rendering the benefit-to-risk ratio unquestionably in favour of aspirin therapy.[4] It is therefore not surprising that all US, European and UK guidelines recommend life-long aspirin therapy in all patients with established cardiovascular disease.[5]

Although aspirin is recommended in all patients indefinitely, in patients who have suffered an ACS, which may or may not have required revascularisation, additional antiplatelet therapy on top of daily aspirin treatment is recommended. Thus, in patients who have had a ST-elevation myocardial infarction (MI) or non-ST-elevation ACS (including unstable angina), and in patients who have undergone PCI, addition of an adenosine diphosphate (ADP) receptor blocker such as clopidogrel, prasugrel (Efient®, Eli Lilly) or ticagrelor (Brilique®, AstraZeneca) is recommended for up to 1 year.[9] Although the ADP receptor blocker is usually discontinued at the end of the year, thus covering the acute phase of thrombotic disease, aspirin is continued indefinitely, thus maintaining antiplatelet coverage into stable CAD.

Antiplatelet therapy in stroke

Stroke is a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15–30% being permanently disabled.[10] Although the role of anticoagulation is well established in stroke prevention, the role of aspirin therapy is less clear in this patient group.[11] As such, most recent guidelines do not recommend the use of aspirin in primary prevention, but warrant the use of aspirin cardiovascular prophylaxis (including but not specific to stroke) in individuals whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6–10%).[11]

In patients suffering from atrial fibrillation, aspirin is recommended either on top of or in replacement of anticoagulation in low-risk and some moderate-risk patients. The decision is based on patient preference, estimated bleeding risk if anticoagulated and access to anticoagulation monitoring.[11] For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with aspirin and clopidogrel might be reasonable; the combination offers more protection against stroke than aspirin alone but with increased risk of major bleeding.

Antiplatelet therapy in peripheral arterial disease

Lower-extremity artery disease (LEAD) is a relatively common pathology. The disease is often asymptomatic, with approximately one-third of all LEAD patients in the community presenting with symptoms. A recent study has reported a LEAD prevalence of 18%, with 7% of patients reporting symptoms of intermittent claudication.[12] In the latest meta-analysis by the Antithrombotic Trialists' Collaboration, the incidence of vascular death, non-fatal MI and non-fatal stroke at follow-up was significantly decreased by 23% by antiplatelet drugs in patients with intermittent claudication.[4] It follows that antiplatelet therapy is recommended in patients with symptomatic PAD, with low-dose aspirin (75–150 mg daily) at least as effective as higher daily doses.[13] Moreover, antiplatelet therapy with aspirin is recommended in all patients with angioplasty for LEAD to reduce the risk of systemic vascular events, and dual antiplatelet therapy with aspirin and clopidogrel is recommended for a minimum of 1 month in cases of peripheral revascularisation, after which time clopidogrel may be discontinued but with aspirin prescribed indefinitely.

Defining aspirin response

The efficacy of aspirin to prevent thrombotic events in cardiovascular patients is well established, with > 100 randomised trials having been conducted in high-risk patients and demonstrating a reduction in vascular death of approximately 15% and a further reduction in non-fatal vascular events of approximately 30%.[4] Few drugs have demonstrated similar efficacy, with up to 50 major vascular events avoided per 1000 patients treated for 1 year, at a cost of one to two patients experiencing a major GI bleeding event.[5] Both the benefit and the risk associated with aspirin are attributed to its ability to prevent thrombus formation via inhibition of platelet function.[14]

The best-characterised mechanism of aspirin is acetylation of a key enzyme in platelet function, the cyclo-oxygenase (COX)-1 enzyme. This enzyme transforms arachidonic acid into thromboxane A_2 (TxA_2), a platelet agonist and vasoconstrictor.[15–17] Aspirin is effective in inhibiting platelet activity at doses as low as 20–40 mg per day,[18] and is clinically effective in preventing thrombotic events in daily doses as low as 75 mg with little benefit of higher doses.[5] This is particularly important in view of the fact that though low doses of aspirin appear effective in preventing thrombotic events in patients at risk, the effect on bleeding (especially GI bleeding) has been shown to be aspirin dose dependent.[19] In recent years, it has been shown that even acutely well-managed major bleeding events are associated with worse outcomes in cardiovascular patients, in terms of both major adverse cardiovascular events and mortality.[20,21] It follows that most treatment guidelines advocate the use of the lowest aspirin dose effective in preventing thrombotic complications so as to minimise the risk of major bleeding.[22–25] From this, a need for monitoring of aspirin therapy has emerged and prompted the development and investigation of numerous assays of platelet function.

Platelet function testing in routine clinical practice

Current clinical guidelines do not recommend routine platelet function testing for aspirin in cardiovascular patients.[26–28] Although platelet function testing may be considered in certain contexts, for example 'in patients at high risk for poor clinical outcomes'[27] or if 'a diagnosis of non-compliance is likely to aid management',[26] the general message from both European and US guidelines, as well as from the Working Group on Aspirin Resistance of the International Society on Thrombosis and Haemostasis, is that monitoring of antiplatelet response by platelet function assays should remain restricted to clinical research, and not be introduced in daily clinical practice.

A number of reasons may explain the lack of enthusiasm for platelet function testing in recently published guidelines. These include the lack of consensus on the platelet function assay to be used; on the definition of inadequate platelet response to aspirin; and on the clinical management of patients with insufficient platelet inhibition by aspirin.[14] Although there are a number of platelet function tests (PFTs) available, it remains to be established how best to use these assays, and whether or not adjusting antiplatelet therapy based on these results will improve clinical outcome.

Platelet function assays

A vast array of platelet function assays is available to test the response of platelets to the inhibitory effect of aspirin (*Table 1*). Some assays are laboratory based and require extensive expertise to operate, whereas others have been specifically developed to be point of care. Although some assays study global haemostasis, most platelet function assays target a specific phase of platelet function, from platelet adhesion to platelet activation, secretion and aggregation. Important methodological disparities make the assays unique in the way that they assess platelet responses. For example, some of these assays are carried out in whole blood [including whole-blood aggregometry (WBA), platelet counting, platelet function analyser-100 (PFA-100®; Siemens, Malvern, PA, USA), VerifyNow® Aspirin (Accumetrics Inc., San Diego, CA, USA), Impact-R® (DiaMed, Cresier, Switzerland) and flow cytometry], whereas others require sample preparation [such as light transmission aggregometry (LTA), plasma or serum thromboxane B_2 (TxB_2) measurement], and others can be performed on urine (levels of the TxB_2 metabolite 11-dehydro-TxB_2). There is no official guideline recommending one assay over another, and platelet function testing is not recommended for routine clinical testing in patients requiring aspirin therapy. As a result, many of the available platelet function assays have been used in a research capacity, and part of the uncertainty surrounding the definition and clinical relevance of aspirin resistance is due to the non-interchangeable nature of these assays.

From a pharmacological perspective, the monitoring of aspirin efficacy requires assessment of the ability of aspirin to inhibit its pharmacological target (platelet COX-1), and thus inhibit the conversion from arachidonic acid to TxA_2.[29] This is the accepted measurement of the European Agency for the Evaluation of Medicinal Products to assess the efficacy of aspirin.[30] Assays measuring TxA_2 formation in clotting blood or in aggregating platelet-rich plasma thus appear ideal. However, TxA_2 cannot be easily measured in biological samples as it has a very short half-life in plasma (30–60 seconds).[31] As a consequence, assays measuring stable metabolites of TxA_2, most commonly TxB_2 (in serum/plasma) or 11-dehydro-TxB_2 (in urine), are the most widely used.

From a functional perspective, a multitude of platelet function assays are available to assess platelet responsiveness to aspirin.[32] Some assays require extensive technical expertise and are limited to specialised laboratories, whereas others are point of care and are meant as bedside tools. The assays that use arachidonic acid as the agonist require a functioning COX-1 to convert it to the active TxA_2 molecules which then elicit a platelet response; these are referred to as COX-1-specific (*Table 2*). TxA_2 is a secondary mediator of platelet activation and synergises with other platelet pathways[33] to elicit full platelet responses. Therefore, aspirin therapy can also partly inhibit platelet activation induced by other agonists, such as collagen and epinephrine.[34,35] Platelet function assays based on these agonists have been used to quantify the platelet reactivity of platelets in patients taking aspirin, although these do not specifically assess the pharmacological efficacy of aspirin.[36] These are referred to as COX-1-non-specific assays (see *Table 2*).

Arguably, COX-1-specific assays may capture more faithfully the effect of aspirin on platelets and may therefore be preferable when looking at the pharmacological efficacy of aspirin. Moreover, COX-1-specific assays are directly targeted by aspirin and are not affected by concomitant antiplatelet therapy, whereas COX-1-non-specific and global assays will be influenced by other antiplatelet therapy used (e.g. in cases of dual antiplatelet therapy with aspirin and an ADP receptor blocker, such as clopidogrel).

TABLE 1 Commonly used platelet function assays for assessing the effect of aspirin

Platelet function assay	Principle	Specificity for COX-1	Advantages	Disadvantages
Pharmacological perspective				
Serum/plasma TxB_2	Assessment of the major TxA_2 metabolite in blood, TxB_2, following clotting of whole blood (serum) or aggregation of platelet-rich plasma (plasma)	Almost exclusively dependent on platelet COX-1 activity	Requires small volume of blood	Prone to artefact Non-linear relationship with TxA_2-dependent platelet aggregation
Urinary 11-dehydro-TxB_2	Assessment of the major TxA_2 metabolite in urine, 11-dehydro-TxB_2	Largely dependent on platelet COX-1 activity	Non-invasive Global measure of TxA_2 formation	Non-platelet sources of TxA_2 will also contribute to this measure Relationship to in vivo platelet activity is unknown
Functional perspective				
LTA	Measurement of light transmission in a platelet-rich plasma sample following stimulation with a platelet agonist	*COX-1 specific:* AA-induced *COX-1 non-specific:* collagen-, epinephrine- or ADP-induced	Historical gold standard	Time and labour intensive Requires large volume of blood Non-physiological milieu for platelets
VerifyNow® Aspirin (Accumetrics Inc., San Diego, CA, USA)	Platelet agglutination onto fibrinogen-coated beads in response to agonist stimulation in whole blood	*COX-1 specific:* aspirin cartridge *COX-1 non-specific:* P2Y12 cartridge	Point of care	Expensive Inflexible
PFA-100® (Siemens, Malvern, PA, USA)	High-shear platelet plug formation on a membrane coated with platelet agonists in whole blood	*COX-1 non-specific:* CEPI cartridge CADP cartridge (CEPI more sensitive than CADP for detecting aspirin)	Point of care Easy to use Includes an element of flowing blood	Detects a high number of patients as poor aspirin responders Correlates poorly with other platelet function assays Sensitive to other factors including vWF, platelet reactivity, platelet count and haematocrit

continued

TABLE 1 Commonly used platelet function assays for assessing the effect of aspirin (*continued*)

Platelet function assay	Principle	Specificity for COX-1	Advantages	Disadvantages
WBA	Measurement of impedance between electrodes immersed in whole blood stimulated with an agonist	*COX-1 specific:* AA-induced *COX-1 non-specific:* collagen- or ADP induced	Physiological milieu for platelets	Time and labour intensive Sensitive to artefactual activation (especially due to haemolysis)
Multiplate® (Roche, Munich, Germany)	Automated WBA	*COX-1 specific:* AA-induced *COX-1 non-specific:* collagen- or ADP-induced	Point-of-care assay	Sensitive to artefactual activation (especially due to haemolysis)
Flow cytometry	Fluorescent measurement of platelet activation markers (e.g. P-selectin) and conformational changes in platelet glycoproteins (e.g. PAC-1 for activated GPIIb/IIIa)	*COX-1 specific:* AA-induced *COX-1 non-specific:* collagen- or ADP-induced	Requires small volume of blood Fixation of samples allows for sending to a core laboratory for analysis	Time and labour intensive Requires specialised equipment and operator Expensive
Plateletworks® (Helena Laboratories, Beaumont, TX, USA)	Single-platelet counting in a whole-blood before-and-after stimulation with a platelet agonist	*COX-1 specific:* AA-induced *COX-1 non-specific:* collagen- or ADP-induced	Easy to use Does not require specialised equipment	Poor correlation with other platelet function assays
Impact-R® (DiaMed, Cresier, Switzerland)	Monitoring of platelet adhesion to a polystyrene surface coated with plasma proteins	*COX-1 specific:* addition of AA *COX-1 non-specific:* plate coated with fibrinogen and vWF	Requires small volume of blood Incorporates an element of shear in whole blood	Poor correlation with other platelet function assays
TEG [TEG® (Haemonetics, Braintree, MA) or ROTEM® (Tem International GmbH, Munich, Germany)]	Monitoring of the rate and quality of clot formation	*COX-1 specific:* platelet mapping technology with AA *COX-1 non-specific:* coagulation-based assay	Provides a readout of global haemostasis	Largely platelet insensitive, even with platelet mapping technology

AA, arachidonic acid; CADP, collagen/ADP; CEPI, collagen/epinephrine; GPIIb/IIIa, glycoprotein IIb/IIIa; LTA, light transmission aggregometry; PAC-1, procaspase-activating compound-1; PFA-100®, platelet function analyser-100; ROTEM®, rotational thromboelastometry; T×B_2, thromboxane B_2; TEG, thromboelastography; vWF, von Willebrand factor; WBA, whole-blood aggregometry.

TABLE 2 Categorisation of platelet function assays

Platelet function assays (aspirin): eligible in any population	COX-1-non-specific and global assays of platelet function: eligible in patients on aspirin alone	Platelet function assays (clopidogrel): not eligible to assess platelet responses to aspirin
COX-1-specific assays: TxA_2 • Serum TxB_2 • Plasma TxB_2 • Urinary 11-dehydro-TxB_2 • AspirinWorks® (Corgenix, Broomfield, Co; commercial urinary 11-dehydro-TxB_2 assay) **COX-1-specific assays: AA** • LTA • WBA • Multiplate® • VerifyNow® Aspirin • Platelet count drop (or single-platelet counting) • Plateletworks® (Helena Laboratories, Beaumont, TX; commercial platelet count drop assay) • Thromboelastograph with platelet mapping technology (AA-induced, not ADP-induced) • Impact-R®/CPA (with AA) • AA-induced P-selectin expression (CD62) or GPIIb/IIIa receptor activation (PAC-1) by flow cytometry	**COX-1-non-specific assays** • Collagen- or epinephrine-induced aggregation (either LTA, WBA, Plateletworks® or Multiplate®) • PFA-100® (platelet function analyser with CEPI cartridge) **Global platelet function assays** • Bleeding time • ROTEM® or thromboelastograph (without platelet mapping technology)	**Activation downstream of the P2Y12-ADP receptor** • VASP phosphorylation assay [Biocytex® (Marseille, France) commercially available assay] **ADP-based** • LTA • WBA • Multiplate® • VerifyNow® P2Y12 • PFA-100® [collagen/ADP or INNOVANCE® (Siemens, Malvern, PA, USA) P2Y cartridges] • Platelet count drop (or single-platelet counting) • Plateletworks® (commercial platelet count drop assay) • Thromboelastograph with platelet mapping technology (ADP-induced, not AA-induced) • Impact-R®/CPA (with ADP) • ADP-induced P-selectin expression (CD62) or GPIIb/IIIa receptor activation (PAC-1) by flow cytometry

AA, arachidonic acid; CEPI, collagen/epinephrine; CPA, cone and plate(let) analyser; GPIIb/IIIa, glycoprotein IIb/IIIa; PAC-1, procaspase-activating compound-1; ROTEM®, rotational thromboelastometry; VASP, vasodilator-stimulated phosphoprotein.

Prevalence and natural history of 'aspirin resistance'

When response to aspirin is assessed by COX-1-specific assays, little variability in platelet responses is seen, with almost complete inhibition of TxA_2-dependent platelet aggregation in almost all patients.[36–40] Far greater biological variability in aspirin-induced platelet inhibition has been reported[36,37,39,41,42] when COX-1-non-specific assays have been used to assess platelet inhibition by aspirin. The definition of normal response to aspirin has also lacked standardisation, and insufficient platelet response to aspirin, or 'aspirin resistance', has been reported in various fashions, including tertiles/quartiles of response as well as dichotomisation based on arbitrary cut-off values. Strikingly, the correlation between the results obtained with the various platelet function assays is disappointingly low,[36,37,39,41,42] thus making the studies using different platelet function assays difficult to compare.

Despite the uncertainties surrounding the best way to test for aspirin effects, platelet function assays have provided a number of potential mechanisms to explain some of the variability seen in platelet reactivity in patients taking aspirin.[43,44] As none of these factors fully explain the variability seen in patients, the phenomenon of aspirin resistance is likely to be multifactorial.

In order to assess the efficacy of aspirin, it must be ascertained that the person being assessed has indeed ingested aspirin. However, non-compliance with prescribed aspirin therapy is common and thus compliance needs to be verified.[45,46] Although crucial to the determination of platelet response to aspirin, assessment of compliance is often lacking in studies of aspirin resistance. In a recent report on the use of

secondary prevention drugs in patients with established cardiovascular disease, Prospective Urban Rural Epidemiology (PURE) study investigators found that approximately one-quarter of patients with an indication for aspirin therapy were actually taking it,[47] making assessment of compliance a necessity prior to platelet function testing. In studies where aspirin administration was actively monitored, the majority of patients who were aspirin resistant on initial testing became responsive to aspirin upon retesting following observed ingestion.[46,48] Thus, in fully compliant patients, aspirin resistance may be a rare but important biological phenomenon.[45,49,50] Another important variable to control for in studies of aspirin resistance is the presence of interacting drugs. A well-described interaction between aspirin and NSAIDs such as ibuprofen and naproxen [but not rofecoxib (Vioxx®, Merck Sharpe & Dohme), celecoxib (Celebrex®, Pfizer), meloxicam, acetaminophen or diclofenac] has been shown to have an impact on platelet aggregation responses.[51–54] These drugs prevent aspirin from binding to its target, platelet COX-1. Therefore, current guidelines recommend that concomitant use of NSAIDs with aspirin should be carefully avoided.[23]

Other factors have been consistently associated with altered platelet responses to aspirin. Genetic factors are known to be associated with variability in platelet responses to aspirin.[40] In a large study of over 1800 participants treated with aspirin, heritable factors contributed to 27–77% of variability in platelet function assay results, most importantly in COX-1-non-specific assays, whereas COX-1-specific assays were influenced by less than 2% by heritable factors.[40] Among considerable environmental factors, obesity plays an important role. Indeed, increased waist circumference and higher body mass index have been associated with reduced efficacy of aspirin to inhibit platelets.[48] This is especially important when enteric-coated aspirin tablets are used, as these also further reduce aspirin bioavailability.[48,55] In diabetic patients, aspirin resistance is more common, and platelets have an enhanced sensitivity to platelet agonists, which has been associated with metabolic alterations, oxidative stress and endothelial dysfunction.[56–62]

Finally, recent evidence suggests that accelerated platelet function recovery may be a potential source of variability in platelet responsiveness to aspirin. The most striking example of platelet turnover involvement in platelet responsiveness to aspirin is in patients suffering from essential thrombocythemia (ET), a natural disease model of enhanced platelet generation. In ET, recovery of platelet function occurs within 24 hours despite daily aspirin therapy and is due to the formation of a large number of new uninhibited platelets from megakaryocytes, resulting in an increased rate of platelet turnover.[63–65] The phenomenon is not, however, limited to ET; both in healthy volunteers and in patients suffering from CAD or diabetes, increased platelet turnover has been associated with insufficient platelet inhibition by aspirin.[66–70] Increasing the frequency of aspirin administration to twice daily has been shown to effectively improve the inhibition of platelet function by aspirin in these settings, although the clinical benefit of this therapy modification remains unknown.[63,64,71–73]

Although the characteristics associated with poor response have been explored in detail,[74] it is noteworthy that the different studies have used different platelet function methodologies to explore the determinants of platelet responses. In parallel, a number of different studies have shown platelet function assay results to lack correlation and agreement among themselves, thus identifying different patients as poor responders to aspirin and having different determinants of response.[37,75,76] Which platelet function assay, if any, is the most clinically predictive of future major adverse cardiovascular events remains to be established.[77] As a consequence, the natural history of aspirin resistance remains somewhat uncertain. There is a need to address basic questions on the prognostic and diagnostic utility and cost-effectiveness of platelet function testing in the context of aspirin therapy before testing can be recommended in clinical practice. A number of systematic reviews attempting to address this basic question have been published in recent years. In general, these have failed to sufficiently capture the volume of available evidence or consider the heterogeneous nature of the evidence reviewed. These reviews are explored in more detail as part of the results section of this report (see *Chapter 5*, *Systematic reviews*). As detailed in *Chapter 3*, the aims of this report were to address this question of prognostic and diagnostic utility of platelet function testing in the context of aspirin therapy.

Chapter 2 Decision problem

This project was commissioned to review the evidence currently available on the association between the result of a PFT and the occurrence of clinically relevant cardiovascular and cerebrovascular events, in those patients receiving long-term aspirin therapy for cardiovascular disease or cerebrovascular disease (CVD), and to consider the cost-effectiveness of the use of such tests. Specifically, this entailed (i) determining prognostic utility (whether or not a test is able to distinguish between groups of patients with different average outcome risks, even if it does not accurately predict individual outcome risk); (ii) determining diagnostic utility [if such tests exist, to determine whether or not they have high diagnostic/predictive utility (e.g. sensitivity, specificity and positive and negative predictive values close to 1) in order to determine, for individual patients, if treatment modification should be considered based on the test result]; and (iii) undertaking an exploratory model-based cost-effectiveness analysis.

The commissioning brief produced in 2010 by the National Institute for Health Research (NIHR), prior to this project being funded, was titled *The Diagnostic Utility of Identifying Aspirin Resistance*, and asked:

> *In patients being considered for long term aspirin therapy is there evidence to show which tests of 'aspirin resistance' predict which patients will benefit from a change in management? Should all such patients be assessed and if not in which groups of patients is testing cost-effective?*

The questions posed in the commissioning brief are much wider than those examined by the project that was eventually commissioned and require extensive consideration of the clinical pathway of treating patients with cardiovascular disease or CVD, in whom long-term therapy with aspirin is traditionally viewed as the mainstay of antithrombotic therapy. To review the evidence for each step of the pathway is beyond the scope of the commissioned project. Thus, there are a plethora of questions that cannot be answered by the work undertaken for this project, yet answers are required in order to determine if patients correctly identified as likely to be at higher risk of adverse clinical outcomes while receiving long-term aspirin therapy should have their management changed, and if so, when, and to what alternative therapeutic regimen. These questions include but are not limited to the following:

- If patients could be correctly identified by a PFT as being at greater risk of adverse clinical outcomes than other patients, do such patients gain some benefit, no matter how small, from the aspirin therapy?
- Does platelet function, as measured by a given test, change over time in a given individual, and if so, to what degree, when and why?
- When, if at all, should platelet function testing be undertaken, and should testing be repeated and when?
- At what threshold of risk of adverse outcomes should a change in therapy be considered?
- Which therapeutic regimen should patients considered at high risk be switched to and when?

Some of these questions are intrinsically linked, and there is potentially published evidence related to some of these that could be systematically reviewed in the future.

This project therefore only reviews the available evidence on the prognostic and diagnostic utility of PFTs, applied to patients on long-term aspirin therapy, in order to determine if patient groups or individual patients with high risk of adverse clinical outcomes can be identified correctly. The cost-effectiveness of using these tests is considered through a review of economic evidence and a speculative de novo model-based economic evaluation using, where necessary, clinician-derived assumption-based inputs relating to parts of the clinical pathway outside of the scope of this project for which definitive published evidence was not readily available.

In this context, 'aspirin resistance' is defined as elevated platelet reactivity measured using a PFT. This definition does not specify a threshold for defining elevated reactivity but relies on that specified by the authors of the studies concerned. As such, there is likely to be considerable variability in the characterisation of aspirin resistance employed in individual studies. Based on this definition, the term 'aspirin resistant' is defined as those individuals classified as having elevated platelet reactivity based on the PFT and threshold specified by the authors of the studies, and 'aspirin sensitive' is defined as those not having elevated platelet reactivity based on the PFT and threshold specified by the authors of the studies.

An evaluation of prognostic utility of aspirin resistance requires assessment of whether or not PFTs are able to distinguish between groups of patients with different average risks of clinically important outcomes.

Providing prognostic utility can be demonstrated, an evaluation of the diagnostic/predictive utility of aspirin resistance requires assessment of whether or not PFTs are able to determine, for individual patients, if they are at increased risk of clinically important outcomes and thus warrant consideration of treatment modification.

Chapter 3 Aim of the review

The aims of the review were as follows:

1. To review systematically the evidence relating platelet function testing to the risk of adverse clinical outcome(s) in patients on aspirin therapy with established cardiovascular disease or CVD, or diabetes. More specifically, to determine whether or not different PFTs have prognostic utility or diagnostic/predictive utility with regard to such clinical outcomes.

    i. *Prognostic utility* To establish whether or not any of the available PFTs has prognostic ability, i.e. is able to distinguish between groups of patients with different average outcome risks. For PFTs demonstrating prognostic utility, to explore:
    ii. *Diagnostic/predictive utility* To establish whether or not any of the available PFTs to determine aspirin resistance has sufficiently high diagnostic/predictive utility (e.g. sensitivity, specificity and positive and negative predictive values close to 1) in order to determine, for individual patients, if treatment modification should be considered based on the test result.

2. To review systematically the evidence relating to the economic utility of platelet function testing in patients on aspirin therapy with established cardiovascular disease or CVD, or diabetes.
3. To undertake exploratory, model-based cost-effectiveness analysis of the use of platelet function testing in patients on long-term aspirin therapy with consideration of the potential for populating the model with data based on the results of the systematic review outlined in (1).

Within this report, the methods and results for the aims outlined in (1) are reported in *Chapters 4* and *5* respectively, and those for the aims outlined in (2) are reported in *Chapter 6*. The findings for all aims are discussed in *Chapter 7*.

The protocol for this project was registered with PROSPERO (2012:CRD42012002151) and has been published on the NIHR Health Technology Assessment (HTA) programme website (www.hta.ac.uk/2468). A version of the protocol was also published in the journal *BMC Systematic Reviews*.[78]

Chapter 4 Methods of prognostic and diagnostic utility review

This section describes the methods for the systematic review of the evidence relating platelet function testing to the risk of adverse clinical outcome(s) in patients on aspirin therapy with established cardiovascular disease or CVD, or diabetes.

The review will specifically target studies which relate platelet function testing to clinical outcome in patients with established cardiovascular disease or CVD or diabetes who are being treated with aspirin. Analysis will consider whether or not PFTs have prognostic ability in that they are able to distinguish between groups of patients with different average outcome risks. If demonstrable, analysis will subsequently consider diagnostic/predictive ability, i.e. whether or not given tests have sufficiently high diagnostic/predictive utility to accurately distinguish those individual patients who will have an adverse outcome from those who will not.

A standard systematic review approach was used and is described below.

Selection criteria

Two broad types of study were considered relevant for this review: those studies that provide information on the prognostic or diagnostic/predictive utility of PFTs and those that report prognostic models, in which a PFT is one of multiple prognostic factors predicting clinical outcomes in a population of interest. The selection criteria for each are outlined below.

Prognostic utility and diagnostic utility studies

Types of study
Any prospective primary studies, or systematic reviews of such studies, assessing PFT(s) in relation to clinical outcomes.

Types of participants
Patients aged ≥ 18 years on aspirin (as monotherapy or in combination with other antiplatelet agents), with established cardiovascular disease or CVD, or diabetes. Studies with mixed populations were included as long as data for relevant patients were extractable. Studies with patients on aspirin for peripheral vascular disease were noted.

Setting
Studies in any setting were included.

Technology
Either a COX-1-specific PFT (which measures aspirin response specifically) or a global PFT in patients receiving aspirin as the only antiplatelet therapy. The selection process was guided by the information in *Table 2*.

Outcomes
Clinical outcomes, such as vascular events [non-fatal and fatal ischaemic stroke, TIA, systemic embolism (pulmonary embolism, peripheral arterial embolism), MI, revascularisation procedures]; haemorrhagic events; all-cause mortality; mortality due to vascular events; composite outcomes containing the above [e.g. major adverse cardiac events (MACEs)].

Timing

Reported outcomes had to occur after the undertaking of a PFT and the post-test follow-up period had to be 7 days or longer. Thus, studies performing platelet function testing after clinical events, with no further follow-up after the testing, were excluded (unless the testing was undertaken on stored samples retrieved prior to the clinical event, as this retains the temporal relationship between testing and subsequent outcome occurrence).

Prognostic model studies

Studies reporting prognostic models, in which a PFT was one of multiple prognostic factors predicting clinical outcomes in a population of interest, were eligible for review, in order to examine the contribution of the PFT to the overall performance of the prognostic model, and to establish whether or not predictive accuracy of clinical outcomes was improved by combining test results with other prognostic factors. The following criteria were used to select such studies:

i. Was a statistical model outlined to predict a relevant clinical outcome outlined above?
ii. Did the model include a factor for PFT result or aspirin resistance?
iii. Was the model developed for use in patients aged ≥ 18 years and on aspirin (alone or in combination with another therapy) for established cardiovascular disease or CVD or diabetes?

Searches

The following bibliographic databases were searched:

- The Cochrane Library (Wiley) (issue 4 of 12) [including the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, HTA Database, NHS Economic Evaluation Database (NHS EED) and Cochrane Central Register of Controlled Trials] to April 2012, MEDLINE (Ovid) from 1950 to 2012, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) to 25 April 2012 and EMBASE (Ovid) from 1980 to 2012.

Search strategies combined index and text words encompassing the technologies (platelet function testing) and the patient group (cardiovascular disease, CVD and diabetes), as well as focusing on aspirin resistance. The Zetoc database (The British Library), Conference Proceedings Citation Index and Science Citation Index (Web of Science) were searched for conference proceedings. ClinicalTrials.gov, the UK Clinical Research Network Study Portfolio Database, the World Health Organization International Clinical Trials Registry Platform and the *meta*Register of Controlled Trials were also searched for ongoing studies.

Reference lists of relevant articles, particularly systematic reviews, were hand-searched to identify other potentially relevant articles. Furthermore, a subject expert was used to identify any studies which may not be identified using standard methods.

Restrictions on publication language and date were not applied to the searches.

Copies of the search strategies used in electronic databases can be found in *Appendix 1*.

In addition, abstracts from the following national and international proceedings were hand-searched from 2009 onwards:

- platelet conferences (Platelets International Symposium)
- cardiology conferences (British Cardiovascular Society, American College of Cardiology, European Society of Cardiology, American Heart Association, American College of Chest Physicians)
- stroke conferences (International Stroke Conference, American Stroke Association)

- haematology conferences (British Society for Haematology, International Society on Thrombosis and Haemostasis, International Society for Laboratory Haematology).

Abstracts that were identified were considered for relevance in a similar way to fully published studies/articles.

Search results were entered into reference management software [Reference Manager version 11 (Thomson ResearchSoft, San Francisco, CA, USA)]. Duplicate records were removed by built-in algorithms and subsequent manual checking.

The searches of electronic databases were undertaken in April 2012 and were not updated after this time. A note was made of any additional relevant studies published subsequently that came to the attention of the authors of this report. These studies were not reviewed to avoid bias. A brief comment is made about these studies in *Chapter 5*, *Relevant studies identified after the search cut-off dates*.

Study selection

Study selection was undertaken as a two-step process. Titles (and abstracts where available) in records were initially screened by two reviewers, using prespecified screening criteria. These criteria were kept necessarily broad as it was anticipated that not all relevant information would necessarily be presented in an abstract, and thus the use of stricter criteria was likely to lead to the exclusion of relevant articles at this screen stage. These criteria were based on whether or not the records indicated that articles were about, or likely to be about, platelet function testing; reported, or were likely to report, clinical outcomes measured after a PFT; and were about patients who had or were likely to have cardiovascular/cerebrovascular or diabetic disease and were receiving aspirin therapy.

An additional criterion for conference abstracts was that these needed to be published from 2009 onwards to be retained. Letters to journals were not automatically classed as irrelevant, because often new results relevant to this field are made available through this medium.

Full texts of any potentially relevant articles or those where a decision could not be made were sought. In the second part of the two-step selection process, full-text articles were assessed against the full inclusion criteria by two reviewers independently. Any discrepancies between reviewers were resolved by discussion or by referral to a third reviewer. A copy of the selection form used for this process is available on request.

Both stages of the selection process were piloted prior to full implementation.

At title and abstract screening and for full-text screening, appropriate portions of non-English-language articles were translated where necessary to aid the selection process.

A record was kept of all decisions made, the reason for exclusion from the review at the full-text screening stage, articles that were not obtainable even by The British Library and also cases where decisions could not be made owing to missing information in a paper or abstract. In the case of this last scenario, an e-mail was sent to an author requesting further information.

During the selection process, any study identified that was thought to be of relevance to the cost-effectiveness review was cross-checked against the search results for that review to ensure comprehensiveness.

Assessment of risk of bias

Risk of bias was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved by discussion.

Prognostic and diagnostic/predictive utility

As the review involved assessment of both prognostic and diagnostic/predictive utility, the quality assessment strategy involved using criteria of relevance from both the Quality Assessment of Diagnostic Accuracy Studies (revised tool) (QUADAS-2) guidelines[79] for diagnostic test studies and criteria for checking the quality of prognostic studies suggested by Hayden *et al.*[80]

These criteria were compiled under the five domains outlined below with their corresponding assessment questions.

- Domain 1: patient selection
  - Was a consecutive or random sample of patients enrolled?
  - Was patient selection independent of patient outcomes?
  - Were reasons for any posteligibility exclusions provided?
- Domain 2: PFT
  - If a threshold was used, was it prespecified?
  - How was the threshold derived (e.g. literature cut-off, based on study data)?
  - Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
- Domain 3: outcomes
  - Were the outcomes of interest clearly defined in advance?
  - Were the outcome results interpreted without knowledge of the results of the PFT?
- Domain 4: study attrition
  - What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost.)
- Domain 5: confounding
  - Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?
  - If there is an adjusted outcome measure [e.g. odds ratio (OR), hazard ratio (HR)], what were the factors that were adjusted for?
  - If a HR was presented, was the proportional hazards assumption met?
  - Was compliance measured?
  - How was compliance measured?
  - Level of compliance.

Prognostic models

If any prognostic models were included, the quality criteria described by Altman[81] were to be used in addition to those of Hayden *et al.*[80] Specific elements to be considered were:

- methods of model development (selection of candidate risk variables, relative weighting, handling of continuous variables)
- internal and external model validations
- study design (prospective/retrospective)
- sample size (considered a priori)
- missing data (quantity, and how missing data were handled in the statistical analysis)
- criteria for inclusion of prognostic factors into the model (adequately described, and whether or not well-known prognostic factors were included regardless of significance).

Any prognostic models identified were to be summarised qualitatively (summarising, for example, included variables, calculation of risk score, predictive accuracy and whether or not the model was validated internally and externally) and quantitatively by extracting performance statistics for calibration (such as observed/expected outcomes) and discrimination (such as sensitivity and specificity) of the model. Similarly, where studies reported the incremental value of including PFTs in prognostic models, these data were to be summarised.

Data extraction

Data extraction was conducted by one reviewer using a standardised, piloted data extraction form, and independently checked by a second. Disagreements were resolved through discussion or referral to a third reviewer.

The data extraction process was necessarily complex owing to the nature and variability of the included studies. Data extraction was undertaken directly into a specially created sheet in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Extensive data related to the following domains were extracted: study design and characteristics; patient characteristics; antiplatelet regimens; PFT utilised; outcome measures and length of follow-up; data required for analyses; statistical methods employed and their appropriateness. Studies were grouped according to whether patients were on monotherapy (aspirin only) or dual therapy (with a second antiplatelet agent such as clopidogrel added to aspirin), in order to distinguish between patients in a stable (monotherapy) or acute phase (dual therapy) of thrombotic disease. Patients who have experienced ACS, or who have undergone PCI, will generally have a second agent added to their therapy for up to 1 year before reverting back to monotherapy. Note that for reasons outlined in *Presentation of results*, only results pertaining to monotherapy studies have been presented in this report.

For further details on data extracted, readers can consult a copy of the database via information presented in *Appendix 4*.

With regard to the data extracted for analysis, details are given in the following section.

Analysis

Data extraction for potential meta-analysis

A key analytical aim was to conduct meta-analysis for each test in relation to each clinical outcome reported by the individual studies. To do this, relevant data reported by the included studies needed to be extracted. Data extraction was conducted independently by two reviewers, and if necessary any differences were resolved via discussion with a third reviewer. If multiple cut-off levels were considered in a study (e.g. to define test 'positive' and test 'negative'), then results were sought for each cut-off reported. Both unadjusted and adjusted results were extracted, as both were considered to be important. Unadjusted results help ascertain the prognostic ability of a test when it is used in isolation. Adjusted results reveal whether or not a test has prognostic utility over and above other prognostic factors; a true causal factor of poor outcome will retain strong prognostic value even after adjustment, and so this further informs the clinical value of a test.

Two groups of summary results were sought during data extraction, as follows.

Prognostic ability: unadjusted and adjusted odds ratios and hazard ratios

The prognostic ability of each test reveals its association with clinical outcome and provides the relative risk between groups defined by test values; for example, the odds of poor outcome in test-positive patients compared with test-negative patients.

For binary outcomes, the reported unadjusted OR and its 95% CI and *p*-value were extracted. If these were not available, data were sought to populate a 2 × 2 table, from which the values could be calculated directly. Any adjusted ORs (with CIs and *p*-values) reported were extracted along with the reported set of adjustment factors that were used.

When the follow-up is longer and/or there are patients lost to follow-up (censored), time-to-event analyses are more appropriate to account for different lengths of follow-up. When time-to-event analyses were reported (e.g. Cox regression analyses, log-rank tests), the unadjusted HR and its 95% CI and *p*-value were sought and extracted. If these were not provided directly, then the methods of Parmar *et al.*[82] to indirectly estimate them from other available data were used. If these were not possible, and a 2 × 2 table was available for a particular time point, the method of Perneger[83] was used; this method assumes that all patients are followed up for the same length of time. Any adjusted HRs (with CIs and *p*-values) reported and the set of adjustment factors that were used were also extracted. For studies using Cox regression, whether or not the proportional hazards assumption had been checked and was considered valid was recorded.

If studies reported results according to the test on its continuous scale, that prognostic result was extracted directly (and so did not force a categorisation). If results were presented for the test categorised into three or more groups (e.g. according to tertiles or quartiles), results for each comparison presented were extracted, but where possible the groups were collapsed down to a binary comparison (to be most comparable with other studies, which generally used a dichotomisation). This collapsing was only possible for calculating unadjusted ORs or unadjusted HRs when 2 × 2 tables could be derived; it was not possible for adjusted results.

If studies provided a 2 × 2 table with one or both groups with a zero cell, then a continuity correction was added to these in order to calculate effect sizes, using the method of Sweeting *et al.*[84] The continuity correction added was 1/(sample size of the opposite group).

Diagnostic/predictive accuracy

If prognostic utility can be demonstrated, an evaluation of diagnostic/predictive utility of aspirin resistance requires assessment of whether or not PFTs are able to determine, for individual patients, if they are at increased risk of clinically important outcomes and thus warrant consideration of treatment modification.

Ordinarily, test accuracy is assessed on ability to distinguish between patients who are subject to a risk factor/carry a marker for disease, etc., and those who are not. However, in the current context of platelet function testing predicting future adverse clinical outcomes, diagnostic utility requires the test to identify the risk factor, and then the risk factor has to be intrinsically linked to the outcome. Thus, the diagnostic utility contains elements of the accuracy of the test in measuring platelet function and the strength of the association between the platelet function and the outcome. Furthermore, there is no single outcome in the current context and the risk of each possible outcome might vary over time. This means that, prior to assessment of diagnostic utility, it is important to have demonstrable association between the marker and outcome(s).

As will be seen in *Chapter 5*, no strong association was identified between any PTF and clinical outcome, thus determination of diagnostic utility is mute. However, where data were available to consider an assessment of diagnostic utility, the presence of these data was noted and they were extracted. Speculative analysis of sensitivities and specificities was undertaken and this is presented in *Appendix 3* along with a description of the relevant analysis methods.

Meta-analysis methods

Once the summary results were extracted for each study and for each test, the clinical experts and researchers met to identify groups of similar patient groups and clinical outcomes across studies. For each patient group and outcome identified, the possibility for meta-analysis was considered; that is, whether or not suitable data were available from multiple studies for the same clinical outcome and test in relation to prognostic ability (relative risk scale: synthesis of ORs or HRs, taking unadjusted and adjusted results separately) and, speculatively, the diagnostic/predictive ability (absolute risk scale: sensitivity and specificity). Where possible, a separate meta-analysis for each cut-off level was considered. The intended methods for any meta-analyses were outlined in the protocol. As a result of the clinical and methodological heterogeneity between studies, pooling of data was determined to be inappropriate even in subgroups of studies employing the same PFT. However, data are presented in this report in forest plots (without the summary estimate) along with some relevant study characteristics highlighting heterogeneity.

Amendments to protocol

Initially the protocol did not specify that studies of patients on dual/triple antiplatelet therapy [i.e. aspirin with additional antiplatelet agent(s)] had to employ an aspirin-specific PFT, rather than any PFT. This was changed prior to study selection and the pertinent platelet function assays are reflected in *Table 2*.

It was originally stated that studies which met all of the inclusion criteria except for reporting clinical outcomes would be noted, as these might provide useful information for cost-effectiveness analysis (e.g. uncertainty around the prevalence of those defined as aspirin resistant from specific assays in specific populations). From very early in the study selection process, the protocol was amended to omit this owing to the very large number of studies being identified and limited benefit of identifying these across all the tests and populations.

These amendments were reported to the NIHR and a revised protocol was submitted.

Presentation of results

Throughout the following sections, our aim has been to highlight the heterogeneity between studies with regard to population, PFT, outcomes and analysis of studies.

Results have therefore been separated according to whether patients were receiving only aspirin as antiplatelet therapy (monotherapy) or aspirin and a second antiplatelet agent (dual therapy) at the time of the PFT. There are a number of reasons for this:

- Populations receiving monotherapy are potentially likely to differ from those receiving dual therapy (e.g. they are less likely to have very recently had an acute cardiovascular event or to be undergoing non-elective PCI).
- The influence of a second antiplatelet agent on an aspirin-specific PFT is unclear.
- The second antiplatelet agent is likely to influence occurrence of clinical outcomes, and occurrence of outcome is fundamental to determination of prognostic utility.
- Resistance to other antiplatelet agents is known, and may affect event rates.

The original intention was to report and analyse studies relating to both patients receiving monotherapy and those receiving dual therapy. It was decided to undertake a stepwise approach to the analysis, starting with monotherapy studies and then moving on to dual-therapy studies; based on the reasons listed above, it is possible that an association between aspirin resistance and clinical outcome may be more apparent within those populations receiving aspirin therapy alone, as it might be more difficult to demonstrate prognostic utility in patients receiving aspirin with additional antiplatelet therapy because of the potential added confounding effect of the other antiplatelet agent.

Furthermore, it is debateable whether or not analysis of studies with dual therapy is warranted in the absence of demonstrated prognostic utility of platelet function testing in patients treated with aspirin as monotherapy. As this criterion was not met (i.e. prognostic utility could not be adequately demonstrated), all results presented in the following sections relate to monotherapy only. However, in the interest of transparency the authors wish for all extracted and analytical data (including those from dual-therapy studies) to be available to readers of this report. The data have been made available through a web portal and further details can be found in *Appendix 4*, including how to access the data.

Monotherapy studies were further defined as those where all, or the vast majority of, patients were on monotherapy *at the time of the PFT*, given that treatment strategies may change over time depending on disease progression. Adding a second agent may affect the rate of clinical events, and this may not be independent of the underlying risk, as higher-risk patients are more likely to be receiving or to commence dual therapy. Where studies have clearly specified where a proportion of patients have at some point during the follow-up period switched therapy or received additional therapy, this information has been extracted. It is, however, possible that not all studies have reported this information.

Populations have been broadly classified as having (i) stable CAD, (ii) stable CVD/stroke, (iii) PAD/peripheral vascular disease (PVD) or (iv) unstable angina (UA)/ACS. Where patients are undergoing elective PCI (PCI) or primary PCI (PPCI), this has also been indicated. Where the population comprises several patient groups, this has been classified as miscellaneous. Note that some acute populations have been included where the PFT was undertaken when patients were on monotherapy.

Results have been separated for different PFTs, and where several thresholds or agonists have been used, this has been indicated. Where different PFTs have been used within the same study, results have been presented in *Chapter 5*, *Studies with more than one test*.

Outcomes have been classified as (i) death, (ii) MACE, (iii) ischaemic/thrombotic or (iv) haemorrhagic/bleeding. A consistent definition for MACE is not used in the literature;[85] for example, it may or may not include stroke. For a composite outcome that includes cerebrovascular complications, the abbreviation MACCE is sometimes used (with the additional 'C' indicating the cerebrovascular component), but again, this is not consistent. Rather than devise a definition of what constitutes MACE or MACCE for this report, studies with a composite outcome of adverse cardiovascular events have been grouped together using the abbreviation MACE. Where stroke has been reported as a separate outcome, this has also been highlighted.

Within the categories of MACE/MACCE there are some inconsistencies between studies in how this has been defined; this has been appropriately highlighted where necessary. The category of 'ischaemic/thrombotic' events is broad and encompasses a number of different events such as revascularisation, angina, bypass surgery, cardiovascular readmission, graft occlusion, MI, etc.

The different outcome measures used in the studies have been summarised as a first step in deciding whether or not pooling is possible and to give an idea of the range of outcome measures used. They have been grouped according to the following: sensitivity and specificity, unadjusted or adjusted ORs, or unadjusted or adjusted HRs. Where HRs or ORs have not been presented but have been calculated for this report, this has been indicated. Additionally, where groups have been collapsed in order to provide a single threshold, this has also been indicated. Note that where outcomes have been reported for different test characteristics (e.g. different agonist, threshold, etc.), not all results will necessarily have been summarised using the same outcome measures.

Odds ratios and HRs provide information on the usefulness of a PFT as a prognostic risk factor. Adjusted ORs or HRs may take into account differences in clinical characteristics, which are linked to adverse events. At the least informative level, articles have only provided a narrative statement regarding the relationship between PFT results and clinical events.

Quality assessment of studies is also clearly presented to aid interpretation of findings.

Owing to the extensive nature of the data extracted from included studies for this project, it was deemed unfeasible to adequately present all the data in this report (even as appendices). The results section of the prognostic utility review in this report contains, where necessary, details of the studies, including the populations studied, test characteristics and quality-related features, and data for key outcomes are presented in illustrative forest plots.

Chapter 5 Results of prognostic utility review

Quantity of research available

The searches resulted in the identification of 16,583 records (after automatic removal of duplicate records) and one further record from checking reference lists of relevant systematic reviews. Manual removal of duplicate records left 13,795 article records. Screening of titles and abstracts in these records indicated that 12,581 were not relevant. Full-text articles of the remaining 1214 were sought. Twenty of these articles were unobtainable and these are listed in *Appendix 5*; 65 were reports of ongoing studies and these are commented on later in this chapter (see *Ongoing studies*); and 1129 full-text articles were obtained for assessment against the inclusion criteria. Nine hundred and thirty-three articles were excluded and these are listed in *Appendix 6*, *Table 85* with reasons for exclusion; 12 of these were excluded because there was insufficient information available to make a decision despite requests by e-mail to the authors for further details (see *Appendix 6*, *Table 86*).

One hundred and ninety-six articles met the inclusion criteria. Of these, 62 contained details of PFT results and clinical outcome data but failed to report the outcome data in relation to the test result, and thus provided no relevant information on prognostic utility of the PFT. These studies are listed in *Appendix 7*.

A further 119 included articles all reported clinical outcome data in relation to the result of one or more PFTs.[46,76,86–202] These articles report the findings of 108 studies that are detailed in the subsequent sections of this report. The remaining 15 articles[203–217] reported systematic reviews and these are described below (see *Systematic reviews*).

A flow diagram presenting the process of selecting studies can be found in *Figure 2*.

Study mapping

As outlined in more detail below (see *Monotherapy*), included studies were separated into categories based on whether enrolled patients were receiving aspirin as their only antiplatelet agent (monotherapy) or aspirin combined with one or more other agents (dual/triple therapy) at the time of the PFT, and by the type of PFT employed in the study. Subcategorisation was undertaken to distinguish studies in which the therapy at the time of platelet function testing remained the same during follow-up from those in which this changed (e.g. patients on monotherapy at the time of testing but subsequently receiving dual therapy). Subjective decision-making was required in some cases where a proportion of patients was receiving a different therapeutic regimen at the time of testing and/or follow-up (e.g. some on monotherapy and some on dual therapy at the time of testing and/or follow-up). If the proportion was considered small ($\leq 5\%$) then these studies were categorised under the therapy of the larger proportion. If large ($\geq 11\%$), then these studies were put into a separate category.

The result of this mapping of studies is shown in *Table 3*.

Of the 108 included studies with test data linked to clinical outcome data, 57 studies reported on a patient group solely or predominantly receiving aspirin as monotherapy at the time of testing,[46,76,86,88,90,92,93,95,99,105,108–110,112,113,115–118,121,123,125,127,128,132,133,135,137,138,142,144–155,159,162–164,166,168,169,171,174,186,187,189,193,195,196,198,201,202] 51 studies reported on a group of patients solely or predominantly receiving dual therapy[87,89,91,94–98,100–102,104,106,111,114,119,120,122,124,126,129–131,134,136,139–141,143,147,150,156–161,165,167,170–173,175–185,188,190,191,192,194,197,199,200] and one study[103,107]

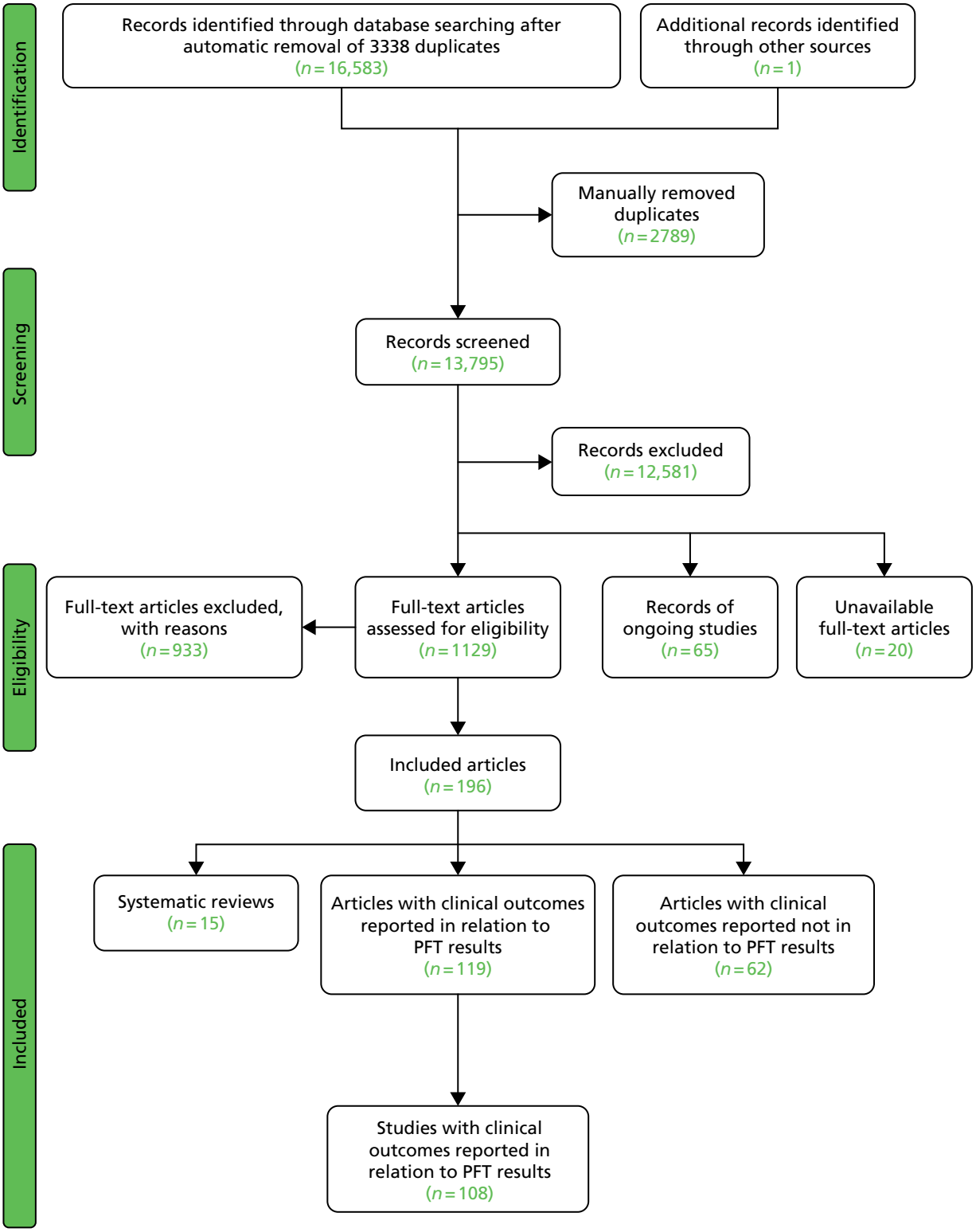

FIGURE 2 Flow diagram showing study selection.

TABLE 3 Mapping of included studies

PFT	LTA	VerifyNow® Aspirin	PFA-100®	Thromboxane metabolites	WBA	TEG	Miscellaneous tests
Monotherapy							
	Studies: 19	Studies: 7	Studies: 21	Studies: 11	Studies: 8	Studies: 3	Studies: 7
				Urinary: 9	*Multiplate®: 1*		
				Serum/plasma: 3	*Impedance: 7*		
				(N.B. One study is both urinary and serum)			
Monotherapy at time of PFT and during follow-up	Abumiyah[95]	Chen[133]	Bevilacqua[118]	Bruno[148] *(urinary)*	*Multiplate®:*	Sahin[168]	Buchanan[152] *[bleeding time by Surgicutt II® (ITC Commercial Group, USA)]*
	Cha[121]	Lee[171]	Boncoraglio[116]	Cotter[46] (*plasma*)	Orta[166]		Grotemeyer[154] *(platelet reactivity test)*
	De Boni[159]	Ozben[86]	Christiaens[127]	Eikelboom[151] *(urinary)*	*Impedance:*		
	Feher[88]		Morawski[144]	Eskandarian[202] *(urinary)*	Gengo[128]		Stejskal[146,198] *[Apact II® (Labitec GmbH, Ahrensburg, Germany) cationic propyl gallate platelet aggregometry]*
	Gum[149]		Poulsen[132]	Thomson[110] *(urinary)*	Mueller[153]		
	Kempfert[113]		Sambola[145]				
	Ohmori[142]		Silver[189,193]				
	Payne[147]						
	Sørensen[155]						
	van der Loo[90]						
	Studies with more than one test						
			Addad[108]	Addad[108] *(urinary)*			
		Gluckman[99]	Gluckman[99]	Gluckman[99] *(urinary)*	Gluckman[99]		
	Linnemann[112]		Linnemann[112]				

continued

TABLE 3 Mapping of included studies (*continued*)

PFT	LTA	VerifyNow® Aspirin	PFA-100®	Thromboxane metabolites	WBA	TEG	Miscellaneous tests
	Lordkipanidzé[162]	Lordkipanidzé[162]	Lordkipanidzé[162]	Lordkipanidzé[162] *(urinary)*	Lordkipanidzé[162]		
					Majeed[117]	Majeed[117]	
	Miyata[164]			Miyata[164] *(serum and urinary)*			
	Schwammenthal[125]						Schwammenthal[125] *(Impact-R®)*
			Sobol[186]		Sobol[186]		
	Tan[174]					Tan[174]	
Monotherapy at time of PFT, proportion on monotherapy and proportion on dual therapy during follow-up	Feng[201]	Chu[105]	Aksu[109]	Eikelboom[195] *(urinary)*			
	Zanow[169]		Campo[123]				
			Hobikoglu[135]				
			Pamukcu[137]				
			Ziegler[150]				
			Fuchs[138]				
	Studies with more than one test						
			Frelinger[76]	Frelinger[76] *(serum)*			Frelinger[76] *(flow cytometry)*
	Modica[187] *[PA-20/200® (Kowa Inc., Tokyo, Japan) test]*		Modica[187]				
Monotherapy at time of PFT, dual therapy during follow-up		Kim[92]	Foussas[115]				
	Studies with more than one test						
					Kaminska[196]		Kaminska[196] *(flow cytometry)*
	Spectre[93,163]						Spectre[93,163] *(Impact-R®)*

PFT	LTA	VerifyNow® Aspirin	PFA-100®	Thromboxane metabolites	WBA	TEG	Miscellaneous tests
Monotherapy or dual therapy							
Monotherapy or dual therapy at time of PFT. Monotherapy, dual therapy or triple therapy during follow-up		Campo[103,107]					
Dual (triple) therapy							
	Studies: 14	Studies: 12	Studies: 14	Studies: 0	Studies: 10 *Multiplate®: 8* *Impedance: 2*	Studies: 3	Studies: 3
Dual therapy at time of PFT and during follow-up	Abumiyah[95] Angiolillo[96,172,188] Aradi[126] Blindt[130] Cuisset[111] Cuisset[143] De Boni[159] Gurbel[122,136] Marcucci[160] Payne[147]	Amoah[91] Ko[182] Kim[194] Lee[171] Lee[200] Lee[87] *(dual/triple)* Marcucci[161] Range[190] Ripley[178] Ryu[170] Saw[119]	Catakoglu[185] Chiu[89] Fateh-Moghadam[181] Foussas[131] Gianetti[141] Grdinic[94] Jacopo[129] Marcucci[139] Pamukcu[140] Smit,[102] Bouman[173] (dual/triple) Ziegler[150]		*Impedance:* Toth[175] Ivandic[114] *Multiplate®:* Eshtehardi[106] Bobescu[176,177,180] Colic[184] Milicic[158,191] Tokgoz[183] Kaymaz[165,167]	Tang[156] Gurbel[197] Sambu[199]	Buch[134] *[Ultegra RPFA-ASA® (Accumetrics,San Diego, CA, USA)]* Vaduganathan[192] *(Ultegra RPFA)*
	Studies with more than one test						
	Breet[98,101,157] Gori[120,124] Marcucci[104] Ko[100]	Breet[98,101,157]	Breet[98,101,157] Gori[120]		Ko[100]		Breet[98,101,157] *(Impact-R®)*
Diabetes (dual therapy)					Kuliczkowski[97,179]		

contained a mixed population of monotherapy and dual therapy. Five studies[95,147,150,159,171] were able to be mapped to both monotherapy and dual therapy categories. Turning to categories of test, LTA and the PFA-100® were the most frequently used tests in included studies, with VerifyNow® Aspirin, thromboxane metabolites and WBA also frequently encountered. Thromboelastography (TEG) was less well represented. Several tests that fell outside of these categories were placed in a miscellaneous category and this included small numbers of studies that employed, for example, tests such as flow cytometry methods and various commercial assays not included in other categories. Proportions of tests used within the monotherapy studies were: LTA (25%, 19 studies[16,88,90,93,95,112,113,121,125,142,147,149,155,159,163,164,169,174,187,201]), VerifyNow® Aspirin (9%, 7 studies[86,92,99,105,133,162,171]), PFA-100® (28%, 21 studies[76,99,108,109,112,115,116,118,123,127,132,135,137,138,144,145,150,162,186,187,189,193]), thromboxane metabolites measurement (14%, 11 studies[46,76,99,108,110,148,151,162,164,195,202]), WBA (10%, 8 studies[99,117,128,153,162,166,186,196]), TEG (4%, 3 studies[117,168,174]) and miscellaneous tests (9%, 7 studies[76,93,125,146,152,154,163,196,198]). The corresponding proportions for dual-therapy studies were: LTA (25%, 14 studies[95,96,98,100,101,104,111,120,122,124,126,130,136,143,147,157,159,160,172,188]), VerifyNow® Aspirin (21%, 12 studies[87,91,98,101,119,157,161,170,171,178,182,190,194,200]), PFA-100® (25%, 14 studies[89,94,98,101,102,120,124,129,131,139–141,150,157,173,181,185]), thromboxane metabolites measurement (0%), WBA (18%, 10 studies[97,100,106,114,158,165,167,175–177,179,180,183,184,191]), TEG (5%, 3 studies[156,197,199]) and miscellaneous tests (5%, 3 studies[98,101,134,157,192]). Note that several studies utilised a range of tests concurrently in the same study population. These are also identified, along with the tests used, in *Table 3*.

Prognostic utility of tests

Population characteristics and quality assessment of studies are presented in the following sections. As outlined in more detail in *Chapter 4*, *Presentation of results*, the structuring of results has been guided by:

- population receiving monotherapy or dual therapy at the time of the PFT
- therapy received after the PFT
- PFT used
- outcome (death, MACE, ischaemic/thrombotic event, bleeding)
- outcome measures presented or calculable [(un)adjusted OR and HR, sensitivity and specificity]; note that sensitivities and specificities are presented in *Appendix 3*.

This is followed by a summary for each PFT. Studies where more than one PFT were performed concurrently are reported in *Studies with more than one test*.

Monotherapy

The tests identified for assessing platelet function in patients on monotherapy (aspirin only) are (i) LTA, (ii) VerifyNow® Aspirin, (iii) measurement of urinary or serum/plasma 11-dehydro-TxB_2 concentrations, (iv) PFA-100®, (v) WBA, (vi) TEG and (vii) other miscellaneous tests.

Light transmission aggregometry

Population and test characteristics

Nineteen studies[88,90,93,95,112,113,121,125,142,147,149,155,159,162,164,169,174,187,201] were identified in this category, four of which were reported in abstract form only,[162,164,169,174] and one as a letter.[88] Populations had CAD (six studies[113,142,149,162,164,201]), CVD/stroke (six studies[88,95,121,125,155,159]) or PAD/PVD (four studies[90,112,147,169]). There were three studies[93,174,187] in patients with UA/ACS; in one of these[93] patients were all undergoing PPCI. None of the studies reported how long patients had had their primary underlying condition for.

In 12 studies[88,90,95,112,121,142,147,155,159,162,164,174] it appeared that patients were exclusively on monotherapy both at the time of the PFT and during follow-up. In two studies,[113,125] around 4% and 5% of patients were on dual therapy (aspirin + clopidogrel) at the time of the PFT. Given the small proportion on dual therapy, these studies have been included in the 'monotherapy' category.

In a further four studies,[149,169,187,201] patients were on monotherapy at the time of the PFT, and around 4%,[149] 25%[169,201] or 45%[187] of patients respectively went on to receive an additional antiplatelet agent (clopidogrel) at some point during follow-up. It is possible that not all studies have reported where a proportion of patients commenced additional therapies during follow-up.

In the study where patients underwent PPCI,[93] patients were on monotherapy at the time of the PFT and all were on dual therapy (aspirin + clopidogrel) during follow-up. This study has been listed separately, as the addition of clopidogrel therapy in all patients may affect the rate of events, and may also be a reflection of underlying population differences compared with the other studies.

Comedications, where reported, included statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrate esters, proton pump inhibitors and dalteparin (Fragmin®, Pfizer). NSAIDs were not permitted (or had to be discontinued within a certain time period) in seven studies;[88,90,112,142,149,159,201] one study[155] stated that drugs known to affect PFTs were discontinued, and there were no details on NSAIDs in the remaining studies.

The number of participants in the studies ranged from 32 to 583 (see *Table 4*). Where reported, mean ages of patients ranged from 60 to 75 years, with most means around the mid to late 60s or early 70s. There were more men than women in 14 out of 15 studies that reported on this,[88,90,93,95,112,121,125,147,149,155,159,163,174,187,201] with proportions of men ranging from 53% to 81%. Only one study[142] included more women (54%). The proportion of patients with diabetes ranged from 11% to 47%, and that of smokers from 5% to 66% (where reported, see *Table 4*). All studies were conducted in hospital settings.

The dose of aspirin ranged between 75 mg/day and 325 mg/day, with the exception of one study[155] where the dose was high, at 1000 mg/day. This study included patients with TIAs or reversible ischaemic neurological deficits. There were no details on dose in one study.[95] Details were variable across studies regarding the length of time patients had been receiving aspirin therapy, with some noting a minimum period and some whether patients were chronic or first-time users, but many giving no details (see *Table 4*). No study stated whether aspirin was provided in enteric or plain form, though one study[93] noted that aspirin was in chewable form.

The main study characteristics are listed in *Table 4* below. Note that in some studies baseline characteristics have been reported only according to resistant/sensitive groups or groups with/without adverse clinical events, rather than for the total study population.

The test performed in 18 out of 19 studies was LTA. Most tests used arachidonic acid as an agonist, with some also using collagen and ADP, and sodium citrate as the anticoagulant (where reported). One study[187] used a variant of LTA, an aggregometer that uses laser light scattering (the PA-200).

Most studies reported no details on the timing of the PFT after aspirin ingestion. One study[125] noted that there were at least 6 hours between aspirin dose and PFT, and three other studies[112,147,149] stated that there were up to 24 hours between aspirin dose and PFT. *Table 5* provides details of test characteristics.

TABLE 4 Population characteristics (LTA, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT and during follow-up										
Abumiya 2011,[95] Japan	144	Mean 66.22 (SD 9.73)	Mono	CVD/stroke	Smokers: 16.7% Diabetes: 22.2%	No	No details	No details	No details	Mean % aggregation stated by groups ± adverse event
Cha 2008,[121] South Korea	107	Mean 64.3 (SD 12.0)	Mono	CVD/stroke	Smokers: 66% Diabetes: 46%	No	100 mg/day	PFT 5 days after being on aspirin	24 or 75	Depending on how tertiles were aggregated
De Boni 2011,[159] Italy	32	Mean/median? 62.8 (range 40–84) for total group (includes patients on monotherapy, dual therapy and clopidogrel only)	Mono	CVD/stroke	No details	No details	100 mg or 200 mg (frequency not stated)	No details	0	Aggregation (AA) ≥ 20%
Feher 2011,[88] Hungary (letter)	281	Mean 64.13 (SD 10.92) sensitive, mean 66.74 (SD 10.17) resistant	Mono	CVD/stroke	Smokers: $n = 78$ (28%) Diabetes: $n = 72$ (26%)	No	100 mg/day	Mean 8.4 (SD 3.6) months	18.1	No details
Feng 2011,[201] China	136	Mean 74.9 (SD 7), range 60–89	Mono (25% dual during follow-up)	CAD	Smokers: $n = 41$ (30%) Diabetes: $n = 37$ (27%)	No details	100 mg/day	No details but not previously on aspirin	No details	Quartiles: aggregation results given for patients with events

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Gum 2003,[149] USA	326	Mean 59 (SD 15) resistant, mean 62 (SD 11) sensitive	Mono (3.7% dual at follow-up)	CAD	*Smokers:* Aspirin resistant ($n = 17$): 0% Aspirin sensitive ($n = 309$): 6% *Diabetes:* Aspirin resistant ($n = 17$): 18% Aspirin sensitive ($n = 309$): 25%	Yes (in 'some'). Elective cardiac catheterisation	325 mg/day	≥ 7 days before enrolment	5.2	Aggregation ≥ 20% (AA), ≥ 70% (ADP). Unclear if resistance based on AA and/or ADP
Kempfert 2009,[113] Germany	59	No details	Mono (5% dual at time of PFT)	CAD	No details	Yes: CABG and combined procedures	500 mg aspirin intravenously postoperatively, then 100 mg/day	No details	28.8	Defined as aspirin resistant if platelet aggregation exceeded the threshold of 30% despite in vitro addition of 25 µM aspirin
Linnemann 2009,[112] Germany	57	Median 67.7 (range 44–90)	Mono	PAD/PVD	Smokers: $n = 31$ (31.6%) Diabetes: $n = 45$ (45.9%)	No	100 mg/day	At least 14 days	3.5	Resistance defined as the maximum aggregation values within the reference range (≥ 78%) despite aspirin medication

continued

TABLE 4 Population characteristics (LTA, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Lordkipanidzé 2011,[162] Canada (abstract)	198	No details	Mono	CAD	No details	No	80–325 mg/day	No details	No details	No details (ORs reported)
Miyata 2011,[164] Japan (abstract)	583	No details	Mono	CAD	No details	No	More or less than 100 mg/day (proportions not stated)	No details	No details	No details (narrative statement regarding event rate and platelet function)
Modica 2009,[187] Sweden	334	Mean 72	Mono (45% dual at discharge)	UA/ACS	Smokers: 21% Diabetes: 20%	No details	75 mg/day	No details	No details	No details (HRs reported)
Ohmori 2006,[142] Japan	136	Mean 75.4 (SD 9.4)	Mono	CAD	Smokers: $n = 7$ (5.1%) Diabetes: $n = 15$ (11%)	No	81 mg (frequency not stated)	No details	No details	Significant event difference noted for upper quartiles compared with others
Payne 2004,[147] UK	54	Mean 69 (SD 8.5)	Mono	PAD/PVD	Smokers: 32% Diabetes: 19%	Yes: carotid endarterectomy	150 mg (frequency not stated)	4 weeks before surgery	0	Aggregation (AA) $\geq 20\%$

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Schwammenthal 2008,[125] Israel	105 (79 eligible for analysis)	Mean 63 (SD 12)	Mono (4% dual at time of PFT)	CVD/stroke	*Smokers:* Good response ($N=40$): current smokers, $n=7$ (18%); past smokers, $n=13$ (33%) Partial response ($N=34$): current smokers, $n=5$ (15%); past smokers, $n=11$ (33%) Complete unresponsiveness ($N=31$): current smokers, $n=8$ (26%); past smokers, $n=5$ (16%) *Diabetes:* Good response ($N=40$): $n=7$ (16%) Partial response ($N=34$): $n=11$ (32%) Complete unresponsiveness ($N=31$): $n=10$ (32%)	No	100 mg (55%) or 325 mg (45%) (frequency not stated)	40% > 1 week before index event	60.7	Aggregation (AA) ≥ 20% (partial and complete unresponsiveness groups aggregated)

continued

TABLE 4 Population characteristics (LTA, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Sørensen 1983,[155] Denmark	41	Mean 58 (range 34–73) based on total population, not stated for aspirin group	Mono	CVD/stroke	No details	No	1000 mg/day	No details	41.5	Platelet hyperaggregability defined as 'secondary aggregation obtained by ADP concentration ≤ 1 µmol/l.' No further details
Tan 2010,[174] China (abstract)	250	Mean 62 (SD 17), range 48–71	Mono	UA/ACS	No details	No details	150–250 mg/day	No details	18.8	Aggregation (AA) ≥ 20%
van der Loo 2011,[90] Switzerland	109	Mean 68.1 (SD 11.4) with events, mean 72.3 (SD 9.7) without events	Mono	PAD/PVD	*Smokers:* Reported by pack-years (1 pack-year of smoking based on someone who had smoked one pack of cigarettes per day, i.e. 20 cigarettes daily for 1 year) With events at follow-up ($n = 66$): 36.4 (SD 38.8) pack-years Without events at follow-up ($n = 43$): 27.9 (SD 28.2) pack-years *Diabetes:* With events at follow-up ($N = 66$): $n = 23$ (35%) Without events at follow-up ($N = 43$): $n = 11$ (26%)	Yes: percutaneous angioplasty	100 mg/day	No details	No details	Mean levels of platelet aggregation shown for groups with and without events

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Zanow 2010,[169] Germany (abstract)	75 and 54 (different aspirin regimens)	No details	Mono (25% dual during follow-up)	PAD/PVD	No details	Yes: endovascular revascularisation, peripheral bypass	100 mg/day or one-off dose postoperatively	No details	Daily aspirin group: 31 One-off aspirin group: 32	Aggregation (AA) ≥ 30%
Monotherapy at time of PFT, dual therapy during follow-up										
Spectre 2011,[93] Israel	54	Mean 59.7	Mono at PFT, all patients on dual post PFT	UA/ACS (undergoing PPCI)	Smokers: 30% Diabetes: 24%	Yes: PPCI	100 mg/day	Previous long-term use of aspirin in 73%	33.3 or 66.7	Depending on whether upper two or lower two tertiles were grouped together to provide a single cut-off

AA, arachidonic acid; SD, standard deviation.

TABLE 5 Test characteristics (LTA, monotherapy)

Study	Details of kit/ manufacturer	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Monotherapy at time of PFT and during follow-up				
Abumiya 2011[95]	MC Medical, Tokyo, Japan	'Citrated blood'	Collagen (2 µM)	No details
			Collagen (5 µM)	
			ADP (1 µM)	
			ADP (10 µM)	
Cha 2008[121]	Model 560 VS (Chrono-log Corporation, Havertown, PA, USA)	Sodium citrate	AA (0.5 mg/ml = 1.6 mM)	No details
			ADP (10 µM)	
De Boni 2011[159]	Chrono-log 700-4 lumi-aggregation systems (Chrono-log Corporation, Havertown, PA, USA)	Sodium citrate (3.2%)	AA (0.5 mM increasing up to 1 mM)	No details
Feher 2011[88] (letter)	LTA (no further details)	No details	No details (reported elsewhere)	No details
Feng 2011[201]	LTA (no further details)	No details	AA	No details
Gum 2003[149]	PAP4 platelet aggregometer (BioData, Horsham, PA, USA)	Sodium citrate (3.8%)	AA (0.5 mg/ml = 1.6 mM)	1–24 hours before blood sampling
			ADP 10 µM	
Kempfert 2009[113]	PAP-4 (moeLab, Berlin, Germany)	Citrate	AA (1 mM)	No details
Linnemann 2009[112]	Behring Coagulation Timer® (BCT®) (Dade Behring, Düdingen, Switzerland)	Sodium citrate (3.2%)	AA (0.5 mg/ml = 1.6 mM)	1–24 hours
Lordkipanidzé 2011[162] (abstract)	LTA (no further details)	No details	AA (1.6 mM)	No details
			ADP (5 µM)	
			ADP (10 µM)	
			ADP (20 µM)	
Miyata 2011[164] (abstract)	LTA (no further details)	No details	AA	No details
			Collagen	
Modica 2009[187]	PA-200	Sodium citrate (0.129 M)	Epinephrine (30 µl of a solution containing 0.1 mg epinephrine)	No details
Ohmori 2006[142]	LTA (no further details) and PA-20 platelet aggregation analyser	Sodium citrate (10%)	Collagen (1 µg/ml)	No details
Payne 2004[147]	PAP4 platelet aggregometer	Trisodium citrate (3.8% wt/vol)	AA (2.5 mM)	< 24 hours
Schwammenthal 2008[125]	PACKS-4 (Helena Laboratories, Beaumont, TX, USA)	'Citrated blood'	AA (1.6 mM)	At least 6 hours before blood sampling
Sørensen 1983[155]	Turbidimetric aggregation (Born method)	No details	ADP (lowest ADP concentration that could produce secondary aggregation)	No details

TABLE 5 Test characteristics (LTA, monotherapy) (*continued*)

Study	Details of kit/ manufacturer	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Tan 2010[174] (abstract)	LTA (no further details)	No details	AA	Unclear: blood samples collected every 2 hours up to 24 hours before and after aspirin administration
van der Loo 2011[90]	APACT 4 aggregometer (Labitec GmbH, Ahrensburg, Germany)	Sodium citrate (3.8%)	Epinephrine (0.1 mM) Collagen (5 µg/ml) ADP (2 mM)	No details
Zanow 2010[169] (abstract)	LTA (no further details)	No details	AA ADP	No details
Monotherapy at time of PFT, dual therapy during follow-up				
Spectre 2011[93]	PACKS-4	Sodium citrate	AA (1.6 mM)	No details

AA, arachidonic acid.

Study design and quality

Results of the risk-of-bias assessment can be found in *Tables 6–9*.

Patient selection was independent of study outcome in all included studies, with the PFT preceding any outcomes (as specified in the study selection criteria). Ten of 19 studies[88,93,112,113,125,147,164,174,187,201] stated that consecutive patients were enrolled into the study. Only one study[159] had clear details on posteligibility exclusion of patients; one criterion for exclusion was no or low compliance.

A predetermined threshold percentage (for platelet aggregation) was given in nine studies; in seven of these[93,121,125,147,149,159,174] the threshold was 20% (with two studies[93,125] defining a further two groups: 20–39% for partial response and ≥ 40% for complete unresponsiveness). In two studies[113,169] the threshold was 30%. The remaining studies stated that quartiles were used,[95,201] described the method of deriving a threshold but not an actual percentage[112,155,187] or gave no details.[88,142,162,164] One study[90] stated mean levels of platelet aggregation only (for groups with and without clinical events). Most studies cited a reference for their threshold or method of derivation; there were no details in seven studies.[88,90,95,142,162,164,201] Only one study[142] gave clear details on blinding of laboratory staff to patient characteristics.

Outcome measures of interest were clearly predefined in all but five studies.[88,113,155,159,169] Four studies[125,142,149,187] had clear details regarding blinding to the PFT results of those assessing outcomes. There appeared to be no loss to follow-up in three studies.[90,121,187] Loss to follow-up was stated in seven studies[93,112,113,125,142,149,155] and ranged from 2% to 57% (see *Table 8*). There were no clear details in nine studies.[88,95,147,159,162,164,169,174,201] The differences in completeness of follow-up may reflect length of follow-up, study design (outcome only followed up in those that had repeat PFTs) or quality of reporting.

Compliance was measured in seven studies.[88,112,113,142,149,159,164] In three studies[88,142,149] this was by a general practitioner (GP) assessment and/or patient interview, but no details on the level of compliance were stated; one patient was excluded on the basis of non-compliance in one of these studies.[142] One study[112] stated that after interview all patients confirmed that they had taken aspirin as directed over the last 14 days.

TABLE 6 Risk of bias, patient selection (LTA, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Monotherapy at time of PFT and during follow-up			
Abumiya 2011[95]	No details	Yes	No details
Cha 2008[121]	Unclear; patients selected from a larger, consecutively enrolled group	Yes	No details
De Boni 2011[159]	No details	Yes	Patients who changed therapy, with low/no compliance, intolerance/allergy to aspirin, contraindications to anticoagulants, who did not attend follow-up
Feher 2011[88] (letter)	Consecutive	Yes	No details
Feng 2011[201]	Consecutive	Yes	No details
Gum 2003[149]	Unclear; patients recruited from consecutive patients presenting to the outpatient clinic	Yes	No details
Kempfert 2009[113]	Consecutive	Yes	No details
Linnemann 2009[112]	Consecutive	Yes	No details
Lordkipanidzé 2011[162] (abstract)	No details	Yes	No details
Miyata 2011[164] (abstract)	Consecutive	Yes	No details
Modica 2009[187]	Consecutive	Yes	No details
Ohmori 2006[142]	No details	Yes	No details
Payne 2004[147]	Consecutive	Yes	Unclear; 38/138 patients excluded before randomisation, but unclear if any would have met the inclusion criteria
Schwammenthal 2008[125]	Consecutive	Yes	No details
Sørensen 1983[155]	No details	Yes	No details
Tan 2010[174] (abstract)	Consecutive	Yes	No details
van der Loo 2011[90]	Unclear (substudy of a trial)	Yes	No details
Zanow 2010[169] (abstract)	No details	Yes	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Spectre 2011[93]	Consecutive	Yes	No details

TABLE 7 Risk of bias, PFT (LTA, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived? (e.g. literature cut-off, based on study data)	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Monotherapy at time of PFT and during follow-up			
Abumiya 2011[95]	No	Quartiles	No details
Cha 2008[121]	Yes (> 20%)	Reference cited[151]	No details
De Boni 2011[159]	Yes (> 20%)	Reference cited[149,218]	No details
Feher 2011[88] (letter)	No details	No details	No details
Feng 2011[201]	No	Quartiles	No details
Gum 2003[149]	Yes (≥ 20% for AA and ≥ 70% for ADP)	No details	No details
Kempfert 2009[113]	Yes (aspirin resistant if platelet aggregation exceeded the threshold of 30% despite in vitro addition of 25 µM aspirin)	Unclear; states that platelet aggregation was measured according to the manufacturers' instructions	No details
Linnemann 2009[112]	Partially; method yes, actual value no. Based on results from group of 20 healthy volunteers. Resistance defined as the maximum aggregation values within the reference range (≥ 78%) despite aspirin medication	In accordance with recommendations given at the 53rd Annual Scientific and Standardization Committee Meeting of the ISTH in Geneva in 2007, the 5th–95th percentile of maximum aggregation measured in duplicate in a group of healthy volunteers ($n = 20$) was considered as the reference range (i.e. 78–96%)	No details
Lordkipanidzé 2011[162] (abstract)	No details	No details	No details
Miyata 2011[164] (abstract)	No details	No details	No details
Modica 2009[187]	Yes (high residual platelet reactivity was defined as a normal CT value even when the subject was taking aspirin)	Reference cited[77]	Unclear ('test results were not accessible by the attending physicians')
Ohmori 2006[142]	No details	No details	Yes; laboratory staff were kept unaware of patient information
Payne 2004[147]	Yes (> 20%)	Reference cited[219]	Unclear; states that 'all personnel involved with the trial were blinded to the nature of the patients' current drug therapy.' However, this may not apply to PFTs
Schwammenthal 2008[125]	Yes (good response < 20%, partial response 20–39%, complete unresponsiveness ≥ 40%)	Reference cited[149]	Unclear; treating physicians and the investigators evaluating the patients were blinded to the results of the platelet function studies

continued

TABLE 7 Risk of bias, PFT (LTA, monotherapy) (*continued*)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived? (e.g. literature cut-off, based on study data)	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Sørensen 1983[155]	Yes (platelet hyperaggregability defined as secondary aggregation obtained by ADP concentration ≤ 1 μM)	Reference cited[220]	No details
Tan 2010[174] (abstract)	Yes (> 20%)	No details	No details
van der Loo 2011[90]	No (mean levels of platelet aggregation shown for groups with and without events)	N/A	No details
Zanow 2010[169] (abstract)	Yes (≥ 30%)	No details	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Spectre 2011[93]	Yes: three groups (good response < 20% aggregation, intermediate 20–40%, poor response > 40%)	No details	No details

AA, arachidonic acid; CT, closure time; ISTH, International Society of Thrombosis and Haemostasis; N/A, not applicable.

TABLE 8 Risk of bias, outcomes and study attrition (LTA, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Monotherapy at time of PFT and during follow-up			
Abumiya 2011[95]	Yes	No details	No details on whether or not there were any missing data
Cha 2008[121]	Yes	No details	No loss to follow-up
De Boni 2011[159]	No	No details	Unclear; patients who did not attend follow-up were excluded from study
Feher 2011[88] (letter)	Unclear	No details	No details
Feng 2011[201]	Yes	No details	No details
Gum 2003[149]	Yes	Those performing follow-up interviews were blinded to aspirin sensitivity status	Follow-up data were available on 97% of patients
Kempfert 2009[113]	No	No details	1/59 patients lost to follow-up. Reason not stated

TABLE 8 Risk of bias, outcomes and study attrition (LTA, monotherapy) (*continued*)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Linnemann 2009[112]	Yes	Unclear; reported events were only considered if they were confirmed by medical reports from GPs or admitting hospitals	Data on clinical outcome available only from patients whose platelet function was assessed twice (57/98). Of the 98, four patients died and 16 had their antithrombotic medication changed, mainly because of an acute cardiovascular event. Not clear what the remaining reasons for dropouts were. This might bias the results though authors state that there was no difference observed in aspirin resistance rates between dropouts and those remaining in the study
Lordkipanidzé 2011[162] (abstract)	Yes	No details	No details
Miyata 2011[164] (abstract)	Yes	No details	No details
Modica 2009[187]	Yes	Yes ('test results were not accessible by the attending physicians')	No loss to follow-up
Ohmori 2006[142]	Yes	Yes; those performing follow-up were unaware of the aspirin sensitivity status	4/136 (three patients who developed atrial fibrillation and one who did not take aspirin were excluded from analysis)
Payne 2004[147]	Yes	Unclear; states that 'all personnel involved with the trial were blinded to the nature of the patients' current drug therapy.' However, this may not apply to PFTs and outcomes	No details
Schwammenthal 2008[125]	Yes	Yes; treating physicians and the investigators evaluating the patients were blinded to the results of the platelet function studies	Follow-up data were available for 81/105 patients (77%)
Sørensen 1983[155]	No	No details	48/83 patients at last follow-up, but proportion of these in aspirin group ($n = 41$) unclear
Tan 2010[174] (abstract)	Yes (though unclear if composite or individual outcomes)	No details	No details
van der Loo 2011[90]	Yes	No details	Appears to be no loss to follow-up for events (though repeat PFTs in decreasing numbers of patients over time)
Zanow 2010[169] (abstract)	No details	No details	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Spectre 2011[93]	Yes	No details	7/63 lost to follow-up at 6 months

GP, general practitioner.

TABLE 9 Risk of bias, confounders (LTA, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Monotherapy at time of PFT and during follow-up						
Abumiya 2011[95]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Cha 2008[121]	Design: N/A Analysis: yes (for OR)	Age (> 70 years), white blood cell count > 15 points on NIHSS, statin therapy, large artery atherosclerotic infarction based on TOAST classification	N/A	No details	No details	No details
De Boni 2011[159]	Design: N/A Analysis: no	N/A	N/A	Yes	Exclusion criterion: those with low/no compliance	No details
Feher 2011[88] (letter)	Design: N/A Analysis: no	N/A	N/A	Yes	'Study drug compliance was assessed by their general practitioners and by personal interview'	No details
Feng 2011[201]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Gum 2003[149]	Design: N/A Analysis: yes (for HR)	Variables in model included age, sex, race, history of tobacco use, diabetes, hypertension, hyperlipidaemia, revascularisation, MI, haemoglobin, platelet count, creatinine, aspirin sensitivity	Yes	Yes	Patient interview both at study enrolment and follow-up	No details

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Kempfert 2009[113]	Design: N/A Analysis: no	N/A	N/A	Yes	If platelets were not sufficiently suppressed (aggregation exceeding the 30% threshold), then the test was repeated after in vitro addition of aspirin (10 µM and 25 µM) to assess whether or not platelets exhibited resistance per se	No details on level. Stated that non-compliance or impaired intestinal uptake excluded by adding in vitro aspirin
Linnemann 2009[112]	Design: N/A Analysis: no	N/A	N/A	Yes	Interview at study commencement and follow-up	'All patients confirmed that they had taken aspirin regularly as directed over the last 14 days.' Assume relates to start of the study
Lordkipanidzé 2011[162] (abstract)	Design: N/A Analysis: unclear if adjusted or unadjusted OR	No details	N/A	No details	No details	No details
Miyata 2011[164] (abstract)	Design: N/A Analysis: appears that adjustment for possible confounders was undertaken, but no adjusted measures presented	No details	N/A	Yes	Interview and by checking plasma concentration of salicylic acid	No details

continued

TABLE 9 Risk of bias, confounders (LTA, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Modica 2009[187]	Design: N/A Analysis: yes (for HR)	Age, sex, diabetes, smoking status, heart failure, atrial fibrillation, baseline glomerular filtration rate, troponin T, platelet aggregation, high residual platelet reactivity, intervention with CABG or PCI	Yes (the assumptions for Cox regression analysis were evaluated by Kaplan–Meier curves for all the variables included)	No details	No details	No details
Ohmori 2006[142]	Design: N/A Analysis: yes (for HR)	Small aggregates, medium aggregates, large aggregates	No details	Yes	By patient interview at enrolment and follow-up	Unclear; one patient who did not take aspirin was excluded from analysis
Payne 2004[147]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Schwammenthal 2008[125]	Design: N/A Analysis: yes (for OR)	Age, NIHSS, diabetes	N/A	No details	No details	No details
Sørensen 1983[155]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Tan 2010[174] (abstract)	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
van der Loo 2011[90]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details (N.B. appears to dismiss non-compliance as a reason for variation on PFTs; stated that 'the variation in platelet response to agonists would imply a high degree of irregularity in taking aspirin, which makes this explanation completely speculative.')
Zanow 2010[169] (abstract)	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Monotherapy at time of PFT, dual therapy during follow-up						
Spectre 2011[93]	Design: N/A Analysis: yes (for HR)	'Variables chosen for inclusion into the model were those that tended to be associated with event-free survival on univariate analysis and age'	No details	No details	No details	No details

N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

A further study[164] assessed compliance by interview and checking of plasma concentration of salicylic acid, but there were no details on level of compliance. One study[159] did not state the method of assessing compliance, but stated that patients with low/no compliance were excluded. In the study by Kempfert *et al.*,[113] the PFT was repeated after in vitro addition of aspirin where platelets were not sufficiently suppressed in order to exclude non-compliance.

Thirteen studies did not appear to undertake any adjusted analyses.[88,90,95,112,113,147,155,159,162,164,169,174,201] Six studies[93,121,125,142,149,187] attempted to adjust for a number of factors. There was some overlap between factors adjusted for (e.g. age), but no study used all the same factors as another. There may be selective reporting in that only variables that showed significance on univariate analysis may have been included in multivariate analyses. One study[142] was unusual in that it adjusted for size of aggregates only.

Overview of outcomes

The main outcome categories reported in the LTA monotherapy studies are shown in *Table 10*. Note that where a study reports MACEs, individual outcomes (e.g. death, stroke) may additionally have been reported separately. There may also be more than one ischaemic/thrombotic outcome reported in the same study. Follow-up periods ranged from 30 days to 3 years.

TABLE 10 Outcomes (LTA, monotherapy)

Study	Death	MACE	Ischaemic/ thrombotic	Bleeding	Length of follow-up
Monotherapy at time of PFT and during follow-up					
Abumiya 2011[95]			✓		1 year
Cha 2008[121]	✓	✓	✓		90 days
De Boni 2011[159]			✓		3 months
Feher 2011[88] (letter)	✓				2 years
Feng 2011[201]				✓	Up to 6 months
Gum 2003[149]	✓	✓	✓		Mean 679 days
Kempfert 2009[113]	✓	✓	✓		12 months
Linnemann 2009[112]		✓	✓		Median 17 months (range 10–37 months)
Lordkipanidzé 2011[162] (abstract)		✓			3 years
Miyata 2011[164] (abstract)		✓			2 years
Modica 2009[187]		✓			Median 44 months (IQR 35–55 months)
Ohmori 2006[142]		✓			Mean 172 days
Payne 2004[147]	✓		✓		30 days
Schwammenthal 2008[125]			✓		Median 11.5 months (range 3.9–19.3 months)
Sørensen 1983[155]			✓		Median 26 months (range 20–36 months)
Tan 2010[174] (abstract)	✓	✓	✓		Mean 360 days (range 0–523 days)
van der Loo 2011[90]			✓		Mean 80 months (range 52–94 months)
Zanow 2010[169] (abstract)			✓		'Long-term'
Monotherapy at time of PFT, dual therapy during follow-up					
Spectre 2011[93]		✓			Up to 15 months

IQR, interquartile range.

Death

Only 6[88,113,121,147,149,174] of the 19 studies reported this outcome, and 5[113,121,147,174,188] reported solely the data needed to populate 2 × 2 tables (*Table 11*).

Figures 3 and *4* present the unadjusted ORs and unadjusted HRs reported for death. None of these were directly available from the publications (except for one HR[149]), but were calculated from other reported data. No study reported adjusted measures. In the study by Payne *et al.* (2004),[147] no patients (out of a total of 54) were found to be aspirin resistant at a threshold of > 20% aggregation, therefore no summary measures could be calculated; one stroke and no deaths occurred in this patient group (follow-up 30 days). Similarly, results could not be presented in forest plots for the study by Tan *et al.*;[174] here the rate of death was 26% in the resistant and 11% in the sensitive group.

In the studies by Cha *et al.*[121] and Gum *et al.*,[149] more deaths occurred in those patients categorised as aspirin resistant; however, none of the unadjusted ORs or HRs were statistically significant. This is also the case for the studies by Feher *et al.*[88] and Kempfert *et al.*,[113] where the extremely wide CIs are a reflection of an adjustment factor used in cases where no events occurred in the aspirin-sensitive groups.

In terms of prognostic utility, although there was a trend towards more events in the aspirin-resistant groups, no study was able to show a statistically significant difference (in CAD or CVD/stroke patients).

Major adverse cardiac events

Eleven[90,93,112,113,121,142,149,162,164,174,187] of 19 studies reported this outcome (*Table 12*).

Note that one study[112] reporting MACEs included death from cardiovascular causes, MI, ACS and stroke, but also amputation or gangrene.

TABLE 11 Outcome measures for reporting death (LTA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/ specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Cha 2008[121]	✓[a]		✓[a]		Number of events reported for three groups: low, intermediate, high ADP aggregation	✓[a]
Feher 2011[88] (letter)	✓[a]		✓[a]			✓[a]
Gum 2003[149]			✓			
Kempfert 2009[113]	✓[a]		✓[a]			✓[a]
Payne 2004[147]					No patients found to be aspirin resistant, therefore not represented in *Figures 3* and *4*	
Tan 2010[174] (abstract)					Some percentages presented, but exact numbers not clear	

a Calculated from data given in the publication.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	OR directly available?	OR (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	No	152.36 (0.03 to 685,812.94)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	No	1.20 (0.23 to 6.15)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	No	1.63 (0.38 to 7.04)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	No	734.18 (0.00 to 9.24e+08)

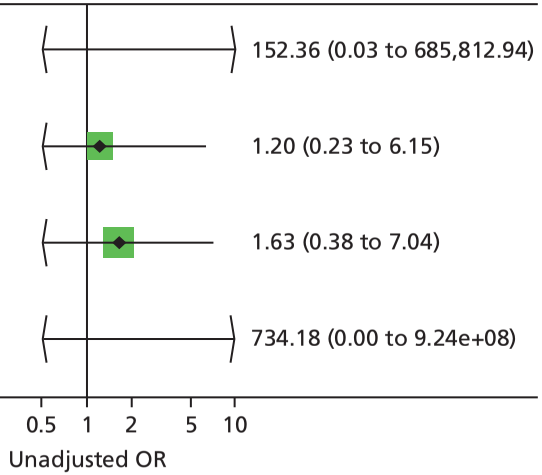

FIGURE 3 Light transmission aggregometry, monotherapy: death, unadjusted ORs. Cha *et al.*[121] results obtained by collapsing tertiles presented into two groups defined by the threshold level shown. AA, arachidonic acid.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	HR directly available?	HR (95% CI)
Gum	2003[149]	USA	326	CAD	Mono	AA (0.5 mg/ml) and ADP (10 μM)	20% for AA, 70% for ADP	Yes	2.98 (0.68 to 13.10)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel[a]	AA (1 mM)	30%	No	138.91 (0.03 to 612,484.56)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 μM)	40%	No	1.19 (0.25 to 5.73)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 μM)	61%	No	1.59 (0.40 to 6.37)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	No	712.16 (0.00 to 8.94e+08)

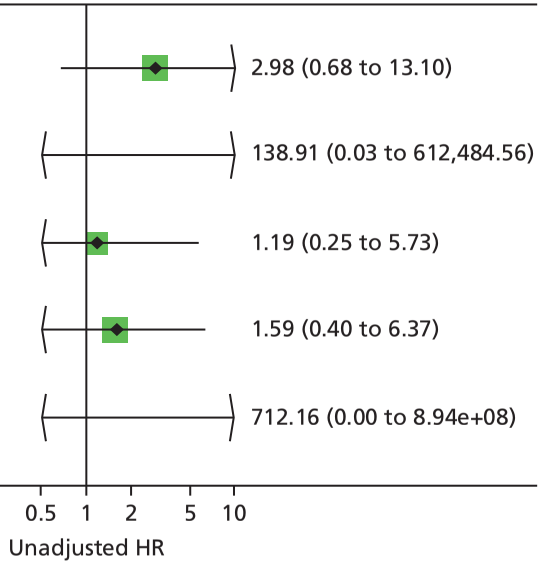

FIGURE 4 Light transmission aggregometry, monotherapy: death, unadjusted HRs. Cha *et al.*[121] results obtained by collapsing tertiles presented into two groups defined by the threshold level shown. AA, arachidonic acid. a, Three patients were on clopidogrel preoperatively, all patients were on aspirin monotherapy post-operatively.

TABLE 12 Outcome measures for reporting MACEs (LTA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/ specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Cha 2008[121]	✓[a]	✓	✓[a]			✓[a]
Gum 2003[149]			✓	✓		
Kempfert 2009[113]	✓[a]		✓[a]			✓[a]
Linnemann 2009[112]	✓[a]		✓[a]			✓[a]
Lordkipanidzé 2011[162] (abstract)	✓					
Miyata 2011[164] (abstract)					Narrative description	
Modica 2009[187]			✓	✓		
Ohmori 2006[142]				✓		
Tan 2010[174] (abstract)					Some percentages presented, but exact numbers not clear	
van der Loo 2011[90]					Mean platelet aggregation values for groups with and without events	
Monotherapy at time of PFT, dual therapy during follow-up						
[a]Spectre 2011[93]	✓[a]		✓[a]	✓		✓[a]

a Calculated from data given in the publication.

The study by Miyata *et al.*[164] reported that no ex vivo measurements for residual platelet function were associated with cardiovascular events (no data presented). In the study by Tan *et al.*[174] the results for total events (MACEs) were unclear, but based on higher numbers of events for death, recurrent MI or thrombosis, it appeared that a greater number of MACEs occurred in the aspirin-resistant group. van der Loo *et al.*[90] reported no significant differences in mean platelet aggregation levels in groups with and without MACEs.

The remaining studies are presented in the forest plots in *Figures 5–8*.

There were 12 unadjusted ORs based on five studies,[93,112,113,121,162] (different agonists, thresholds or time points; see *Figure 5*), 11 of which found no statistically significant differences in event rates; there was also no consistent trend regarding direction of effect. One study[121] found a statistically significant result for one of two thresholds, with more events in the aspirin-resistant group in a CVD/stroke population, but this result was based on a non-aspirin-specific agonist (ADP) and the threshold was derived by collapsing tertiles. Most ORs were not directly available from the studies (with the exception of one[162]).

The one statistically significant OR[121] remained so after adjustment, although it moved very close to 1 (see *Figure 6*). There were no further adjusted ORs.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Spectre	2011[93]	Israel	54	ACS	Mono before, dual post PCI	AA (1.6 mM)	40%	6 months	No	0.86 (0.22 to 3.28)
Spectre	2011[93]	Israel	54	ACS	Mono before, dual post PCI	AA (1.6 mM)	20%	6 months	No	1.92 (0.46 to 8.10)
Spectre	2011[93]	Israel	54	ACS	Mono before, dual post PCI	AA (1.6 mM)	40%	15 months	No	0.70 (0.21 to 2.28)
Spectre	2011[93]	Israel	54	ACS	Mono before, dual post PCI	AA (1.6 mM)	20%	15 months	No	1.00 (0.31 to 3.19)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%		No	95.61 (0.02 to 446,265.84)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	AA (1.6 mM)	Not stated	ADP 20 µM	Yes	1.25 (0.51 to 3.06)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	AA (1.6 mM)	Not stated	ADP 10 µM	Yes	1.10 (0.30 to 4.06)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	AA (1.6 mM)	Not stated	AA	Yes	2.80 (0.52 to 15.18)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	AA (1.6 mM)	Not stated	ADP 5 µM	Yes	0.80 (0.13 to 4.80)
Cha	2008[121]	The Republic of Korea	107	CVD/ stroke	Mono	ADP (10 µM)	40%		No	2.43 (0.51 to 11.52)
Cha	2008[121]	The Republic of Korea	107	CVD/ stroke	Mono	ADP (10 µM)	61%		No	4.70 (1.51 to 14.66)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	AA (0.5 mg/mL)	78%		No	0.10 (0.00 to 233,406.63)

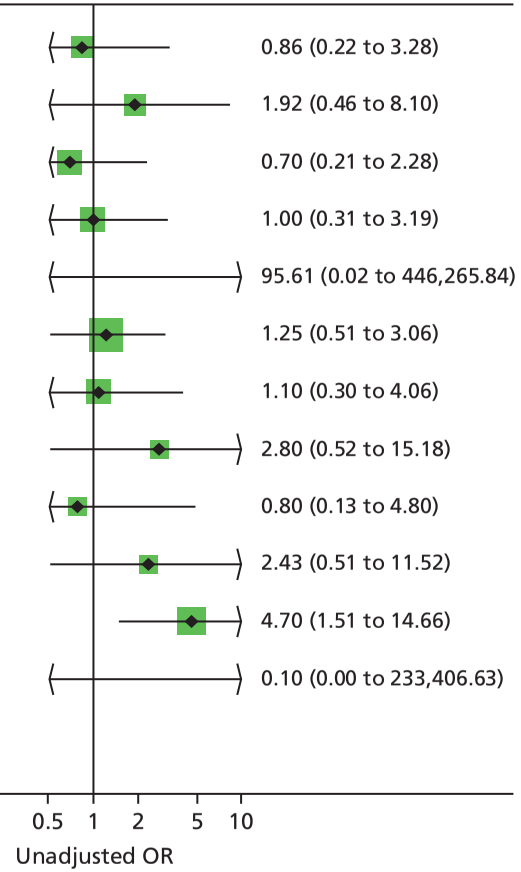

FIGURE 5 Light transmission aggregometry, monotherapy: MACEs, unadjusted ORs. AA, arachidonic acid.

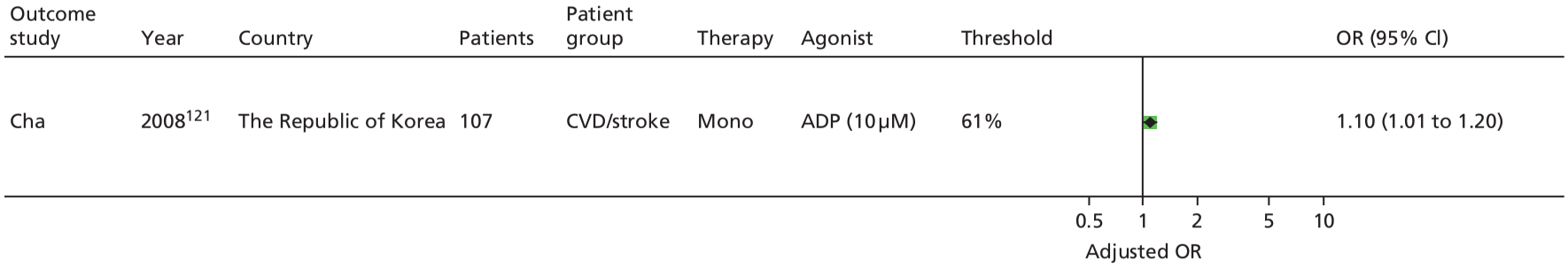

FIGURE 6 Light transmission aggregometry, monotherapy: MACEs, adjusted ORs.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%		No	90.10 (0.02 to 412,361.03)
Cha	2008[121]	The Republic of Korea	107	CVD	Mono	ADP (10 µM)	61%		No	4.07 (1.48 to 11.22)
Cha	2008[121]	The Republic of Korea	107	CVD	Mono	ADP (10 µM)	40%		No	2.30 (0.52 to 10.21)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	AA (0.5 mg/ml)	78%		No	0.11 (0.00 to 226,495.64)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	40%	15 months	No	0.75 (0.29 to 1.94)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	20%	15 months	No	1.00 (0.40 to 2.48)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	40%	6 months	No	0.87 (0.27 to 2.84)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	20%	6 months	No	1.78 (0.49 to 6.49)
Modica	2009[187]	Sweden	334	UA/ACS	Mono	Epienephrine (0.1 mg)	Fourth vs. first quartile		Yes	2.00 (1.21 to 3.32)
Gum	2003[149]	USA	326	CAD	Mono	AA (0.5 mg/ml) and ADP (10 µM)	20% for AA, 70% for ADP		Yes	3.12 (1.10 to 8.87)

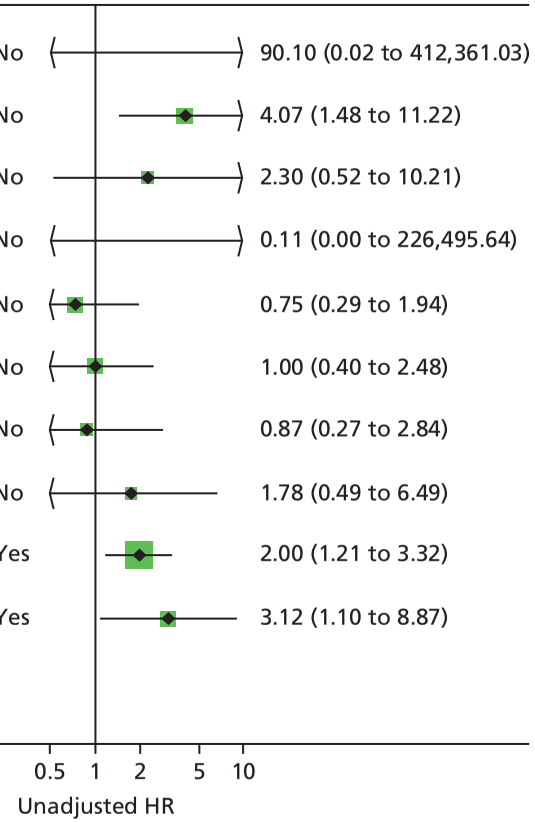

FIGURE 7 Light transmission aggregometry, monotherapy: MACEs, unadjusted HRs. AA, arachidonic acid.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR (95% CI)
Gum	2003[149]	USA	326	CAD	Mono	AA (0.5 mg/ml) and ADP (10 µM)	20% for AA and 70% for ADP		4.14 (1.42 to 12.06)
Ohmori	2006[142]	Japan	136	CVD/stroke	Mono	Collagen (1 µM)	Fourth quartile vs. others	12 months	7.76 (1.71 to 35.15)
Ohmori	2006[142]	Japan	136	CVD/stroke	Mono	Collagen (1 µM)	Fourth quartile vs. others	Entire follow-up	2.32 (0.89 to 6.03)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	20–40% vs. < 20%		7.10 (1.31 to 38.39)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before, dual post PCI	AA (1.6 mM)	> 40% vs. < 20%		8.50 (1.44 to 50.29)
Modica	2009[187]	Sweden	334	UA/ACS	Mono	Epinephrine (0.1 mg)	Fourth vs. first quartile		1.10 (0.64 to 1.91)

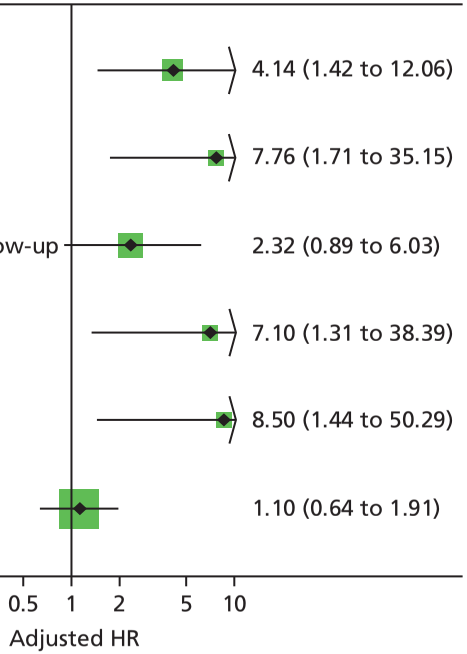

FIGURE 8 Light transmission aggregometry, monotherapy: MACEs, adjusted HRs. AA, arachidonic acid.

There were 10 unadjusted HRs (based on six studies,[93,112,113,121,149,187] see *Figure 7*), all calculated from other data presented in the articles. Three showed statistically significant results (more events in the aspirin-resistant group).[121,149,187] All three included different populations (CAD, CVD/stroke and UA/ACS).

Based on the three studies where an unadjusted HR was calculable, one HR[149] remained statistically significant after adjustment (see *Figure 8*); two previously non-significant results[93] became statistically significant and one previously significant result became non-significant.[187] Of one further study included,[142] one of two results was statistically significant (more events in the aspirin-resistant group).

Based on adjusted measures, there was a consistent trend towards more MACEs in the resistant groups, with some results showing statistical significance. However, this is based on a subsample of studies only (5 of 19 studies[93,121,142,149,187]), and the choice of adjustment factors and inclusion of certain factors into the models may have affected results. Note that two[93,187] of the five studies contributing to these results were in UA/ACS patients, which may differ from the majority of stable populations, and in one study[93] all patients were on dual therapy after the PFT.

Ischaemic/thrombotic events

Thirteen studies[88,90,95,112,113,121,125,147,149,155,159,169,174] reported additional ischaemic/thrombotic events (*Table 13*).

Seven of 13 studies[90,95,112,147,159,169,174] did not provide data which would have allowed their representation in forest plots. There was also heterogeneity across outcome measures (e.g. MI, UA, restenosis, etc.). Many of these measures are also captured in the MACEs described above.

In the study by Abumiya and Houkin[95] there appeared to be a trend for more events (recurrent cerebral infarction) to occur in higher quartiles of platelet aggregation, but no statistical significance could be shown. The numbers in Tan *et al.*[174] were unclear, but it appears that a higher percentage had a recurrent MI or thrombosis in the aspirin-resistant group. van der Loo *et al.*[90] looked at differences in intrapatient variability of platelet aggregation between groups with and without restenosis or occlusion; no evidence for a difference was found (at adjusted *p*-value level). Zanow *et al.*[169] found that long term there was a poorer patency rate for aspirin-resistant patients, but this was not statistically significant.

The study by De Boni *et al.*[159] provided no useful information, as no patients were classified as aspirin resistant and no events occurred. Similarly, in the study by Payne *et al.*[147] no patients were classified as aspirin resistant; there was one stroke (in a group of 54 patients). Linnemann *et al.* assessed a number of ischaemic thrombotic outcomes, but the exact numbers in the aspirin-resistant and aspirin-sensitive groups were unclear; only 2 out of 57 patients were classified as aspirin resistant.

Twelve unadjusted ORs were presented based on four studies[88,113,121,155] (different outcomes, thresholds) (*Figure 9*). All were calculated for this report. CIs were generally very wide and all but one showed no statistical significance, though there was a trend towards more events occurring in the aspirin-resistant groups.

A different study[125] presented an adjusted OR for two thresholds, one of which was statistically significant (*Figure 10*).

Fourteen unadjusted HRs based on five studies[88,113,121,149,155] were presented (*Figure 11*). Again, all but one showed no statistical significance, though there was a trend towards more events in the aspirin-resistant groups. No adjusted HRs were presented.

TABLE 13 Outcome measures for reporting ischaemic/thrombotic events (LTA, monotherapy)

Study	Outcome	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up							
Abumiya 2011[95]	Recurrent cerebral infarction					Results for quartiles represented graphically. Could not extract data from forest plots	
Cha 2008[121]	Non-fatal stroke	✓[a]		✓[a]			✓
	MI	✓[a]		✓[a]			✓[a]
De Boni 2011[159]	Ischaemic events/ clinical relapses					No patient classified as aspirin resistant. No events occurred	
Feher 2011[88] (letter)	Stroke and/or TIA	✓[a]		✓[a]			✓
	UA	✓[a]		✓[a]			✓[a]
	MI	✓[a]		✓[a]			✓[a]
	Peripheral arterial occlusion with revascularisation	✓[a]		✓[a]			✓[a]
Gum 2003[149]	CVA			✓			
	MI			✓			
Kempfert 2009[113]	Stroke	✓[a]					✓[a]
Linnemann 2009[112]	Peripheral arterial revascularisation					Numbers in aspirin-resistant and aspirin-sensitive groups not clear	
	PTA/stenting						
	Bypass surgery or TEA						

Study	Outcome	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Payne 2004[147]	Stroke					No patients classified as aspirin resistant	
Schwammenthal 2008[125]	mRS score ≥ 2 or death during follow-up		✓				
	Recurrent ischaemic event						
Sørensen 1983[155]	Stroke or death	✓[a]		✓[a]			✓[a]
Tan 2010[174] (abstract)	Recurrent MI or thrombosis					Some percentages presented, but exact numbers not clear	
van der Loo 2011[90]	Restenosis or reocclusion					Intrapatient variability of platelet aggregation between groups with and without events	
Zanow 2010[169] (abstract)	Patency after reconstruction					No numerical data	

CVA, cerebrovascular accident; mRS, modified Rankin scale; PTA, percutaneous transluminal angioplasty; TEA, thoracic epidural analgesia.
a Calculated from data given in the publication.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Any outcome	No	1.90 (0.90 to 4.02)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µm)	61%	MI	No	85.28 (0.00 to 2,275,607.50)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µm)	40%	MI	No	28.35 (0.00 to 1.30e+09)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI (no PCI)	No	0.01 (0.00 to 8.07e+10)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI with PCI	No	2.71 (0.76 to 9.64)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µm)	40%	Non-fatal stroke	No	145.06 (0.00 to 6.12e+09)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µm)	61%	Non-fatal stroke	No	14.55 (1.55 to 136.84)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	PAO with revascularisation	No	0.01 (0.00 to 5.32e+10)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	Stroke	No	95.61 (0.02 to 446,265.84)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Stroke and/or TIA	No	1.53 (0.40 to 5.88)
Sørensen	1983[155]	Denmark	41	CVD/stroke	Mono	ADP (?)	1 µmol/l	Stroke or death	No	2.92 (0.59 to 14.41)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	UA	No	0.81 (0.17 to 3.78)

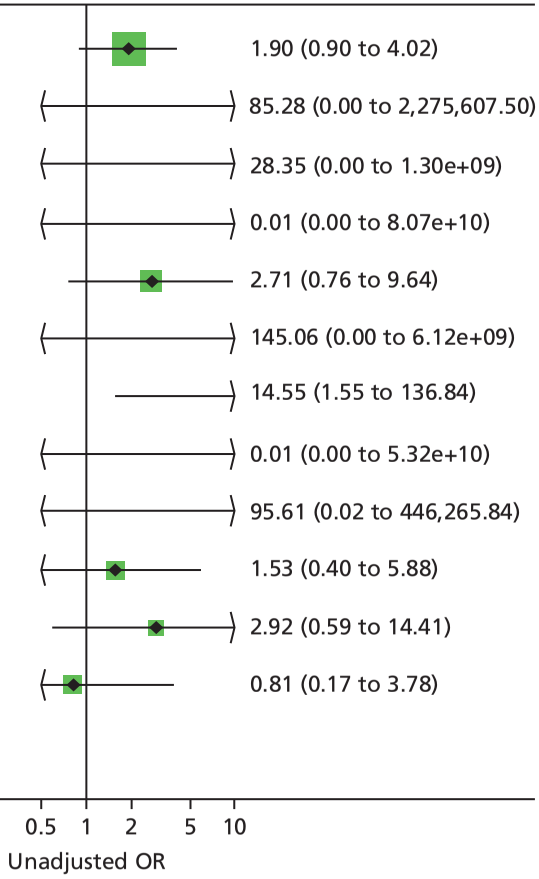

FIGURE 9 Light transmission aggregometry, monotherapy: ischaemic/thrombotic events, unadjusted ORs. AA, arachidonic acid; PAO, peripheral arterial occlusion.

FIGURE 10 Light transmission aggregometry, monotherapy: ischaemic/thrombotic events, adjusted ORs. AA, arachidonic acid; mRS, modified Rankin scale.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Gum	2003[149]	USA	326	CAD	Mono	AA (0.5 mg/ml) and ADP (10 µM)	20% for AA, 70% for ADP	CVA	Yes	5.44 (0.60 to 49.40)
Gum	2003[149]	USA	326	CAD	Mono	AA (0.5 mg/ml) and ADP (10 µM)	20% for AA, 70% for ADP	MI	Yes	1.91 (0.25 to 14.66)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	MI	No	83.62 (0.00 to 2,209,387.50)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	MI	No	28.18 (0.00 to 1.29e+09)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI (no PCI)	No	0.01 (0.00 to 8.10e+10)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI with PCI	No	2.64 (0.77 to 9.03)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	Non-fatal stroke	No	13.45 (1.50 to 120.31)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	Non-fatal stroke	No	140.43 (0.00 to 5.89e+09)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	PAO with revascularisation	No	0.01 (0.00 to 5.35e+10)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	PAO with revascularisation	No	1.79 (0.92 to 3.48)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	Stroke	No	90.10 (0.02 to 412,361.03)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Stroke and/or TIA	No	1.52 (0.41 to 5.61)
Sørensen	1983[155]	Denmark	41	CVD/stroke	Mono	ADP (?)	1 µmol/l	Stroke or death	No	2.61 (0.62 to 10.91)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	UA	No	0.82 (0.18 to 3.68)

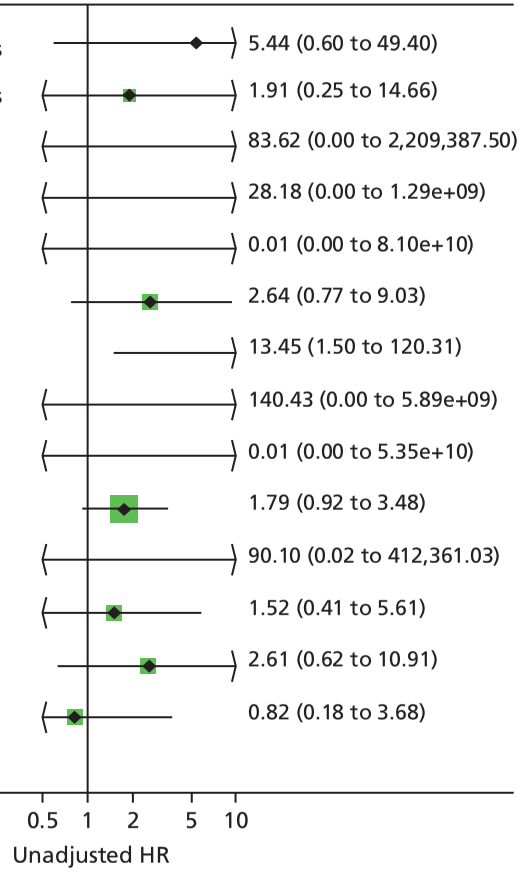

FIGURE 11 Light transmission aggregometry, monotherapy: ischaemic/thrombotic events, unadjusted HRs. AA, arachidonic acid; CVA, cerebrovascular accident; PAO, peripheral arterial occlusion.

Overall, the trend towards more events in the aspirin-resistant group was consistent, but most results were not statistically significant. These results were also consistent with those of the studies not presented in the forest plots. Interestingly, there were three studies where no (or a very small proportion of) aspirin-resistant patients were identified.[112,147,159]

Bleeding events

Only one study[201] reported bleeding events (GI bleeds) (*Table 14*).

Of the four patients with bleeds, three were in the lowest platelet aggregation quartile (values of 2.7%, 6.75% and 9.12%). The threshold value for the lowest quartile was 9.81%. The remaining patient had a value of 11.2% (not stated which quartile). This is consistent with the assumption that GI bleeds are more likely to occur in aspirin-sensitive patients, but the small number of events precludes any firm conclusions.

Summary: light transmission aggregometry monotherapy

Nineteen studies were identified in this category.[88,90,93,95,112,113,121,125,142,147,149,155,159,162,164,169,174,187,201] There were differences in patient populations, though most appeared to have stable disease; note that although there were only three studies[93,174,187] with acute (UA/ACS) populations, two of these[93,187] contribute substantially to the MACE results. There was heterogeneity across studies in terms of specific patient characteristics (e.g. smoker, diabetic, comedications, etc.).

There was a lack of detail in reporting of relevant quality criteria, making an overall judgement on risk of bias difficult. Additionally, studies that do report relevant information may be more open to criticism. Lack of detail related in particular to loss-to-follow-up information, blinding and details of compliance. No study provided details on all relevant quality criteria. There were differences in threshold and method of deriving the threshold for defining aspirin resistance, but the most consistent was a threshold of 20% (seven studies[93,121,125,147,149,159,174]). Only one[142] and four[125,142,149,187] (of 19) studies respectively gave clear details on blinding to patient characteristics or PFT results. Measurement of compliance was undertaken in seven studies,[88,112,113,142,149,159,164] but there was a lack of detail on the results or consequences of this; it appears that in two studies[142,159] patients were excluded on the basis of low/no compliance. Some studies provided adjusted analyses; there was overlap but no consistency in factors adjusted for.

Six studies[88,113,121,147,149,174] reported on differences in deaths between aspirin-resistant and aspirin-sensitive groups; there was a trend towards more events in the aspirin-resistant group (based on four studies[88,113,121,149]), but no significant differences were shown in any.

Eleven studies reported on MACEs.[90,93,112,113,121,142,149,162,164,174,187] There was a trend towards more events in the aspirin-resistant groups, but unadjusted measures found mostly statistically non-significant results. Five of seven results (based on five studies[93,121,142,149,187]) using adjusted measures were statistically significant and the trend was consistent with the unadjusted results; however, this was based on a subset of studies,

TABLE 14 Outcome measures for reporting bleeding (LTA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/ specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Feng 2011[201]					Aggregation values presented for individual patients (according to quartiles for some)	

different adjustment factors and two[93,187] (of five[93,121,142,149,187]) studies in an acute population, which may not be representative of the majority of populations receiving aspirin monotherapy.

Thirteen studies reported additional ischaemic/thrombotic events.[88,90,95,112,113,121,125,147,149,155,159,169,174] Again, there was a trend towards more events in the aspirin-resistant group, but the vast majority of results (mainly unadjusted measures) were not statistically significant. Results of 7 of the 13 studies[90,95,112,147,159,169,174] could not be presented in forest plots, but results were consistent (i.e. non-significant).

There was only one study reporting GI bleeds;[201] this found a trend for more aspirin-sensitive patients to have more bleeds, but this was based on only four events (in 136 patients).

Note that not all studies reporting the relevant outcomes could be presented in the forest plots; the results of those studies not included in the forest plots were in the main consistent with those included or did not add much useful information. It should also be noted that some studies contributed several results to the forest plots as they presented results or could be analysed for different thresholds. Although no results have been pooled, the visual impact of these forest plots might influence how the overall results are perceived. Given the large amount of heterogeneity between the studies in terms of quality criteria, threshold, population, test characteristics (agonists), aspirin dose, etc., it was not possible to compare results across studies. Despite the heterogeneity and lack of many statistically significant results, the direction of prognostic effect appears to be largely consistent with there being more events in aspirin-resistant patients (ORs and HRs usually > 1). This suggests that LTA is a potential prognostic factor, but this is only a qualitative judgement on the evidence available; meta-analysis was not possible owing to the heterogeneity, and therefore a firm quantitative conclusion regarding whether or not LTA is prognostic is not currently possible.

Summary: light transmission aggregometry

- Nineteen studies were identified with mainly stable populations.
- The most frequently reported threshold was 20% platelet aggregation.
- A lack of detail in reporting of quality criteria, particularly around loss to follow-up, blinding and details (and implications) of compliance, hampered an overall risk-of-bias assessment.
- Heterogeneity in outcomes, patient groups and types of reported statistics meant that meta-analysis was not considered appropriate.
- Adjusted results were rarely presented, and thus the additional prognostic value of the test over other prognostic factors is difficult to ascertain.
- Despite clinical heterogeneity between studies, there was an overall consistent trend for more events to occur in the 'aspirin-resistant' group for all relevant outcomes (death, MACEs, ischaemic/thrombotic events); however, most results were not statistically significant.
- There were more statistically significant results (more events in the resistant arm) using adjusted measures for MACEs, but these were based on only five studies.
- One study reporting GI bleeds found a trend for more GI bleeds in 'aspirin-sensitive' patients, but this was based on only four events (in 136 patients).

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Population and test characteristics

Seven studies[86,92,99,105,133,162,171] were identified in this category, one[162] of which was reported in abstract form only. Populations were mainly classified as having CAD (three studies)[99,133,162] or CVD/stroke (two studies).[86,171] One study[105] was in patients with UA/ACS, and one[92] was in patients with severe CAD undergoing CABG. Six studies did not report for how long patients had had their underlying condition; one study[171] stated time from cerebral infarction to randomisation [≤ 90 days: 37 patients (31.1%); 91–364 days: 33 patients (27.7%); ≥ 365 days: 49 patients (41.2%)].

In six studies[86,99,105,133,162,171] it appeared that patients were exclusively on monotherapy both at the time of the PFT and at follow-up. In the remaining study,[92] patients were on monotherapy at the time of the PFT, and on dual therapy [+ ticlopidine (Ticlid®, Sanofi Winthrop)] during follow-up.

Comedications across the studies included, where reported, ACE inhibitors, beta-blockers, angiotensin receptor blockers, calcium channel blockers, statins, oral anticoagulants and lipid lowering agents. NSAIDs were not permitted in four studies[86,92,133,171] and were taken by 28 out of 314 (9%) patients in another,[105] while one study[99] stated that 'concurrent nonsteroidal anti-inflammatory drug use did not correlate with the presence of aspirin non-responsiveness defined by this method at either time point'. There were no details in one study.[162]

The number of participants in the studies ranged from 106 to 468 (see *Table 15*). Mean ages were mainly reported by group (resistant/sensitive) and ranged from 61 years to 70 years. Overall, there were more men than women in the studies, with proportions of men ranging from 50% to 85%. All studies were conducted in hospital settings. The proportion of smokers ranged (where reported) from 11% to 39% and that of diabetics from 21% to 56%.

The dose of aspirin ranged from 75 to 325 mg/day. Four studies[86,105,133,171] noted a minimum period (between 1 and 4 weeks) for which patients needed to have been taking aspirin; there were no details in the remaining studies. Two studies[99,133] stated that aspirin was provided in enteric form (in 65% of patients in one study[133]). There were no details in the remaining studies.

The main study characteristics are listed in *Table 15*. Note that in some studies baseline characteristics have been reported only according to resistant/sensitive groups, rather than for the total study population. All studies used the commercially available VerifyNow® Aspirin test kit (*Table 16*), which uses arachidonic acid as an agonist. Four studies noted the timing of the PFT after aspirin ingestion; this was between 1 and 4 hours,[86] between 2 and 30 hours,[133] up to 24 hours[171] or on the same day.[92] There were no details in the remaining studies.

Study design and quality

Patient selection was independent of outcome in all studies, as all patients with an available PFT were followed up. Two studies[99,171] stated that consecutive patients were enrolled. Two studies[92,99] provided details on posteligibility exclusions; one of these[99] reported that the study population was deemed to be representative of the eligible population.

As this was a commercial test with a manufacturer-recommended threshold, it was assumed that all studies used the same threshold even where not stated. No study gave clear details on whether or not the undertaking and interpretation of the PFT was blinded to patient characteristics. Outcomes were defined in advance in all studies, and there were details in four studies[86,99,105,133] regarding the blinding of outcome assessment (to the results of the PFT). Proportions of missing data were reported in four studies and were less than, or around, 1%[105,133] and up to 14%[171] and 32%.[99] Longer follow-up times did not correspond to greater loss to follow-up.

TABLE 15 Population characteristics (VerifyNow® Aspirin, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT and during follow-up										
Chen 2007,[133] China	468	Mean 66.7 (SD 10.2) resistant, mean 63.2 (SD 11.7) sensitive	Mono	CAD	*Smokers:* Resistant ($N = 128$): $n = 14$ (10.9%) Sensitive ($N = 340$): $n = 44$ (14.1%) *Diabetes:* Resistant ($N = 129$): $n = 50$ (39.1%) Sensitive ($N = 340$): $n = 117$ (34.4%)	No	80–325 mg/day Mean 114.4 mg (SD 42.2 mg) sensitive, mean 102.0 mg (SD 17.8 mg) resistant	At least 4 weeks	27.4	Resistance defined as ARU ≥ 550. No details for derivation of threshold
Chu 2010,[105] New Zealand	314	Mean 67.1 (SD 12.75) resistant, mean 70.1 (SD 11.8) sensitive	Mono (11% dual during follow-up – people who underwent PCI)	UA/ACS	Smokers: $n = 7$ (23.3%) resistant, $n = 38$ (13.4%) sensitive Diabetes: $n = 10$ (33.3%) resistant, $n = 60$ (21.1%) sensitive	PCI in 11% CABG in 2.9%	75–300 mg/day	At least 4 weeks	9.6	Resistance defined as ARU ≥ 550. No details for derivation of threshold

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Gluckman 2011,[99] USA	229	For patients with ≥ 1 occluded SVG ($n = 70$): mean 63 (range 55–72) For patients with patent SVG ($n = 159$): mean 63 (range 57–71)	Mono	CAD	Smokers: $n = 52$ (22.7%) Diabetes: $n = 84$ (36.7%)	Yes: CABG	325 mg/day	No details	No details	Resistance defined as ARU ≥ 550. Derivation according to manufacturer's instructions
Lee 2010,[171] The Republic of Korea	119 (244 enrolled; split into mono and dual therapy) All population characteristics based on 119 (mono group)	Mean 62.8 (SD 10.0)	Mono	CVD/stroke	Smokers: $n = 44$ (37%) Diabetes: $n = 46$ (38.7%)	No	100 mg/day	At least 2 weeks	10.9	Resistance defined as ARU ≥ 550
Lordkipanidzé 2011,[162] UK (abstract)	198	No details	Mono	CAD	No details	No	80–325 mg/day	No details	No details	No details
Ozben 2011,[86] Turkey	106	Mean 64.9 (SD 14.6)	Mono	CVD/stroke	Smokers: $n = 41$ (38.7%) Diabetes: $n = 36$ (34%)	No	100 mg/day	At least 1 week	33	Resistance defined as ARU ≥ 550. Derivation according to manufacturer's clinical studies using optical aggregometry as the comparison standard

continued

TABLE 15 Population characteristics (VerifyNow® Aspirin, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT, dual therapy during follow-up										
Kim 2011,[92] The Republic of Korea	220	Mean 65.1 (SD 10.8) resistant, mean 63.9 (SD 8.8) sensitive	Mono (all patients on dual during follow-up)	MI (CABG)	*Smokers:* Aspirin responders ($N = 181$): $n = 58$ (32%) Aspirin non-responders ($N = 39$): $n = 7$ (17.9%) *Diabetes:* Aspirin responders ($N = 181$): $n = 89$ (49.2%) Aspirin non-responders ($N = 39$): $n = 22$ (56.4%)	Yes: CABG	100 mg/day	No details	17.7	Resistance defined as ARU ≥ 550. Derivation manufacturer's reference value

ARU, aspirin reaction unit; SD, standard deviation; SVG, saphenous vein graft.

TABLE 16 Test characteristics (VerifyNow® Aspirin, monotherapy)

Study	Details of kit	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Monotherapy at time of PFT and during follow-up				
Chen 2007[133]	VerifyNow® Aspirin	No details	AA	Between 2 and 30 hours
Chu 2010[105]	VerifyNow® Aspirin	3.2% citrate	AA	No details
Gluckman 2011[99]	VerifyNow® Aspirin	No details	AA	No details
Lee 2010[171]	VerifyNow® Aspirin	No details	AA	Up to 24 hours
Lordkipanidzé 2011[162] (abstract)	VerifyNow® Aspirin	No details	No details	No details
Ozben 2011[86]	VerifyNow® Aspirin	3.2% citrate	AA	Between 1 and 4 hours
Monotherapy at time of PFT, dual therapy during follow-up				
Kim 2011[92]	VerifyNow® Aspirin	No details	AA	Aspirin administered on day of test

AA, arachidonic acid.

It was not stated whether or not the proportional hazards assumption was met in the two studies[105,133] that reported HRs. Three studies[86,105,133] reported adjusted measures and the factors adjusted for were listed; there was little similarity between the adjustment factors. Four studies[86,99,105,171] stated that compliance was assessed (pill counts; ascertained by nurse, verified with patients). Only one study[171] gave details on the actual level of compliance: six patients were excluded at 4 weeks and a further six at 6 months owing to poor drug compliance (12/119 in total).

Full details are provided in *Tables 17–20*.

TABLE 17 Risk of bias, patient selection (VerifyNow® Aspirin, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Monotherapy at time of PFT and during follow-up			
Chen 2007[133]	No details	Yes	No details
Chu 2010[105]	No details	Yes	No details
Gluckman 2011[99]	No details	Yes	Patients where SVG patency not assessed or those not on aspirin monotherapy. Authors stated that the study population was representative of patients undergoing isolated CABG surgery based on comparison with the Society of Thoracic Surgeons National Database
Lee 2010[171]	Consecutive	Yes	No details
Lordkipanidzé 2011[162] (abstract)	No details	Yes	No details
Ozben 2011[86]	Consecutive	Yes	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Kim 2011[92]	No details	Yes	300 patients assessed for eligibility; 75 did not meet inclusion criteria, five declined to participate

SVG, saphenous vein graft.

TABLE 18 Risk of bias, PFT (VerifyNow® Aspirin, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Monotherapy at time of PFT and during follow-up			
Chen 2007[133]	Yes (ARU ≥ 550)	No details	No details
Chu 2010[105]	Yes (ARU ≥ 550)	No details	Unclear: the clinical team managing the patients was blinded to aspirin resistance status
Gluckman 2011[99]	Yes (ARU ≥ 550)	Manufacturer's instructions	No details
Lee 2010[171]	Yes (ARU ≥ 550)	Manufacturer's instructions	No details
Lordkipanidzé 2011[162] (abstract)	No details	No details	No details
Ozben 2011[86]	Yes (ARU ≥ 550)	Manufacturer's instructions	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Kim 2011[92]	Yes (ARU ≥ 550)	Manufacturer's instructions	No details

ARU, aspirin reaction unit.

TABLE 19 Risk of bias, outcomes and study attrition (VerifyNow® Aspirin, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Monotherapy at time of PFT and during follow-up			
Chen 2007[133]	Yes	Yes. Personnel responsible for data collection were not aware of aspirin responsiveness results. Hospital charts were analysed to ascertain whether or not the events qualified for the definition of the end point	4/464 (0.9%) patients lost to follow-up, one in the aspirin-resistant group, three in the aspirin-sensitive group
Chu 2010[105]	Yes	Yes. The clinical team managing the patients was blinded to aspirin resistance status	2/312 lost to follow-up (death during index hospitalisation)
Gluckman 2011[99]	Yes	Yes. Images were analysed by two blinded reviewers (98% concordance) with a third reviewer adjudicating as necessary	65/229 not included at 6 months
Lee 2010[171]	Yes	No details	17/119 lost to follow-up [reasons: consent withdrawal (4), poor drug compliance (12), miscellaneous (1)]
Lordkipanidzé 2011[162] (abstract)	Yes	No details	No details
Ozben 2011[86]	Yes	Yes. Personnel responsible for data collection were not aware of aspirin responsiveness results	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Kim 2011[92]	Yes	No details	No details

TABLE 20 Risk of bias, confounders (VerifyNow® Aspirin, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Monotherapy at time of PFT and during follow-up						
Chen 2007[133]	Design: N/A Analysis: yes (for HR)	Diabetes, prior MI, haemoglobin levels	No details	No ('Compliance to aspirin therapy was not ascertained by pill count or salicylate level monitoring')	N/A	N/A
Chu 2010[105]	Design: N/A Analysis: yes (for HR)	Troponin-T (other non-significant factors were removed from model)	No details	Yes (before enrolment)	Aspirin dose and compliance were verified with patients before enrolment	No details
Gluckman 2011[99]	Design: N/A Analysis: no	N/A	N/A	Yes	Pill counts at each postoperative encounter	No details
Lee 2010[171]	Design: N/A Analysis: no	N/A	N/A	Yes	Counted all returned medications after 4 weeks of treatment and calculated compliance to the trial medications. Patients with poor compliance were defined as those who missed ≥ 25% of 4-week prescribed doses	12/119 noncompliant: six did not undergo follow-up PFT after 4 weeks of treatment owing to poor drug compliance; six excluded after having the follow-up PFT at 4 weeks owing to poor drug compliance
Lordkipanidzé 2011[162] (abstract)	Design: N/A Analysis: unclear whether adjusted or unadjusted OR	No details	N/A	No details	N/A	N/A

continued

TABLE 20 Risk of bias, confounders (VerifyNow® Aspirin, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Ozben 2011[86]	Design: N/A Analysis: yes (for OR)	Age, sex, NIHSS, prior stroke, comorbidities (hypertension, diabetes, hyperlipidaemia, coronary heart disease, renal failure)	N/A	Yes	Ascertained by nurse charts	No details
Monotherapy at time of PFT, dual therapy during follow-up						
Kim 2011[92]	Design: N/A Analysis: no	N/A	N/A	No details	N/A	N/A

N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale.

Overview of outcomes

The most frequently reported outcome in studies using VerifyNow® Aspirin was MACEs (four studies[92,105,133,162]), followed by other ischaemic/thrombotic events (three studies[92,99,133]), death (two studies[86,92]) and bleeding events (two studies[92,171]). Outcomes and follow-up periods are shown in *Table 21*.

Death

Two studies[86,92] reported this outcome (*Table 22*).

Only two[86,92] of seven studies reported deaths and the different outcome statistics are shown in *Figures 12–14*. One study (Ozben *et al.*[86] in patients with CVD/stroke) found a statistically significant OR and HR (greater number of deaths in the aspirin-resistant group) for both in-hospital and 2-year mortality. The OR (2-year mortality) remained statistically significant when adjusted for age, sex, National Institutes of Health Stroke Scale (NIHSS), prior stroke and comorbidities (hypertension, diabetes, hyperlipidaemia, coronary heart disease, renal failure). Only one death (in the aspirin-sensitive group) occurred in the study by Kim *et al.*[92] in patients undergoing CABG, and no significant difference could be shown.

TABLE 21 Outcomes (VerifyNow® Aspirin, monotherapy)

Study	Death	MACEs	Ischaemic/ thrombotic events	Bleeding	Length of follow-up
Monotherapy at time of PFT and during follow-up					
Chen 2007[133]		✓	✓		Mean 379 (SD 200) days
Chu 2010[105]		✓			> 30 days and up to 6 months
Gluckman 2011[99]			✓		6 months
Lee 2010[171]				✓	4 weeks
Lordkipanidzé 2011[162] (abstract)		✓			3 years
Ozben 2011[86]	✓				2 years
Monotherapy at time of PFT, dual therapy during follow-up					
Kim 2011[92]	✓	✓	✓	✓	Responders: mean 9.8 (SD 10.5) days; non-responders: mean 10.1 (SD 10.8) days

SD, standard deviation.

TABLE 22 Outcome measures for reporting death (VerifyNow® Aspirin, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Ozben 2011[86]	✓[a]	✓	✓[a]			✓[a]
Monotherapy at time of PFT, dual therapy during follow-up						
Kim 2011[92]	✓[a]		✓[a]			✓[a]

a Calculated from data given in the publication.

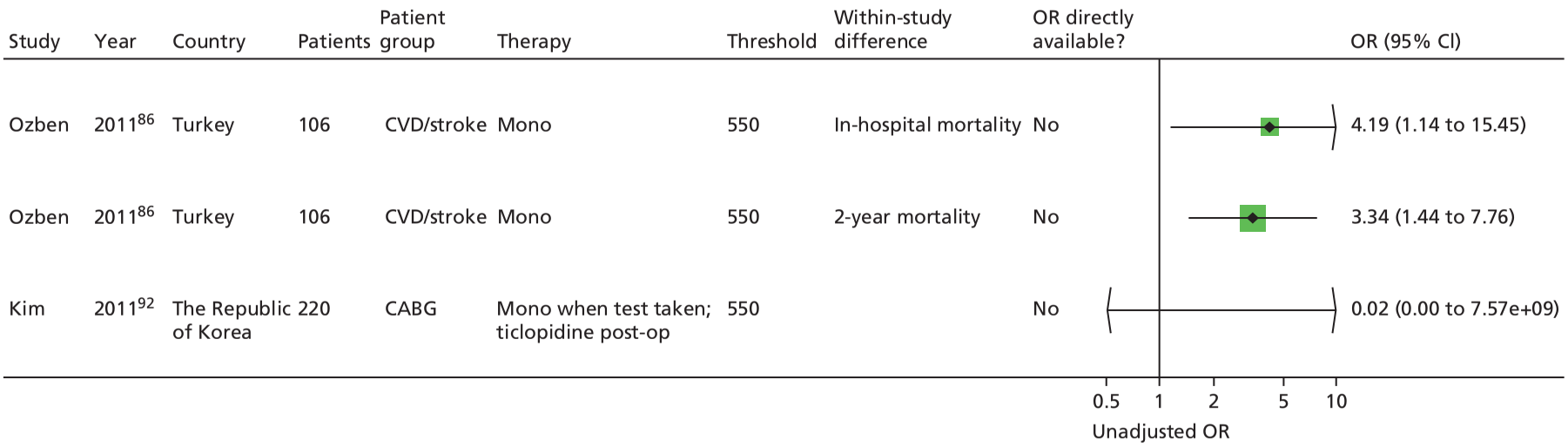

FIGURE 12 VerifyNow® Aspirin: death, unadjusted ORs.

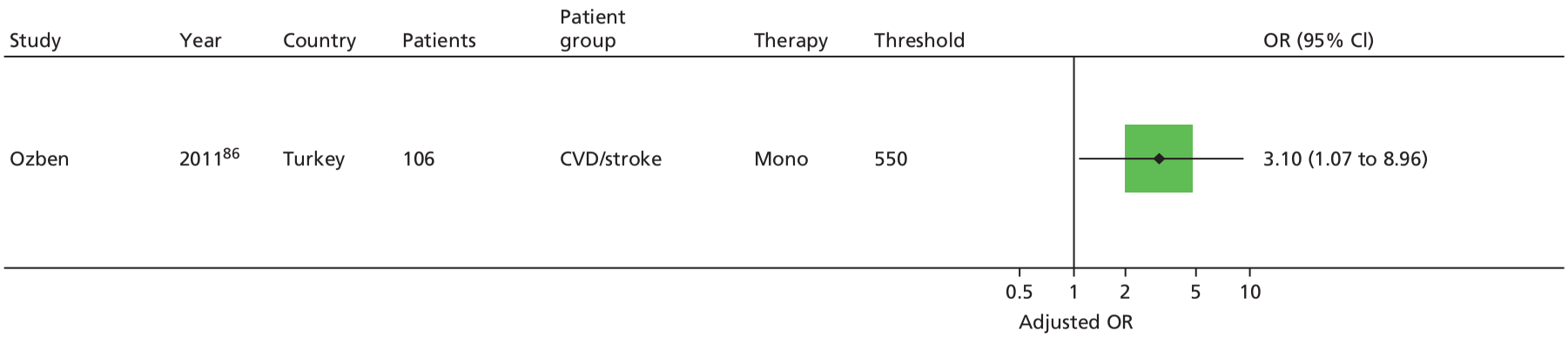

FIGURE 13 VerifyNow® Aspirin, monotherapy: death, adjusted ORs.

FIGURE 14 VerifyNow® Aspirin, monotherapy: death, unadjusted HRs.

Major adverse cardiac events

Four studies[92,105,133,162] reported this outcome (*Table 23*).

Four[92,105,133,162] out of seven studies reported this outcome, and the different outcome statistics are shown in *Figures 15–17*. The studies by Chen *et al.*[133] and Chu *et al.* (for five out of seven subgroups)[105] found a statistically significant difference between groups, with more events in the resistant group (unadjusted OR). Two further studies[92,162] reported more events in the sensitive group, but there were no statistically significant differences. No study reported adjusted ORs. The pattern was similar for unadjusted HRs, though with statistically significant results for five out of seven subgroups (Chu *et al.*[105]) and a statistically significant result, with more events in the resistant group, also presented for the population undergoing CABG in the study by Chen *et al.*[133] Note that the unadjusted HR is not statistically significant compared with the unadjusted OR (Chen *et al.*[133] CAD population); given the relatively long follow-up period (mean 379 days), the HR could be considered the more useful outcome statistic. Adjusted HRs were available for three out of seven subgroups (Chu *et al.*[105] and Chen *et al.*[133] CAD population); these were all statistically significant, with more events in the resistant group. Note that the factors adjusted for in the two studies are completely different (troponin-T only in the study by Chu *et al.*;[105] diabetes, prior MI and haemoglobin levels in the study by Chen *et al.*[133]).

Thus, any statistically significant results relate to a greater number of events in the resistant group; however, not all outcome statistics (particularly adjusted HR) have been reported for all four studies/subgroups, so there is some missing information.

TABLE 23 Outcome measures for reporting MACEs (VerifyNow® Aspirin, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Chen 2007[133]	✓[a]		✓	✓		✓[a]
Chu 2010[105]	✓[a]		✓/✓[a]	✓		✓[a]
Lordkipanidzé 2011[162] (abstract)	✓					
Monotherapy at time of PFT, dual therapy during follow-up						
Kim 2011[92]	✓[a]		✓[a]			✓[a]

a Calculated from data given in the publication.

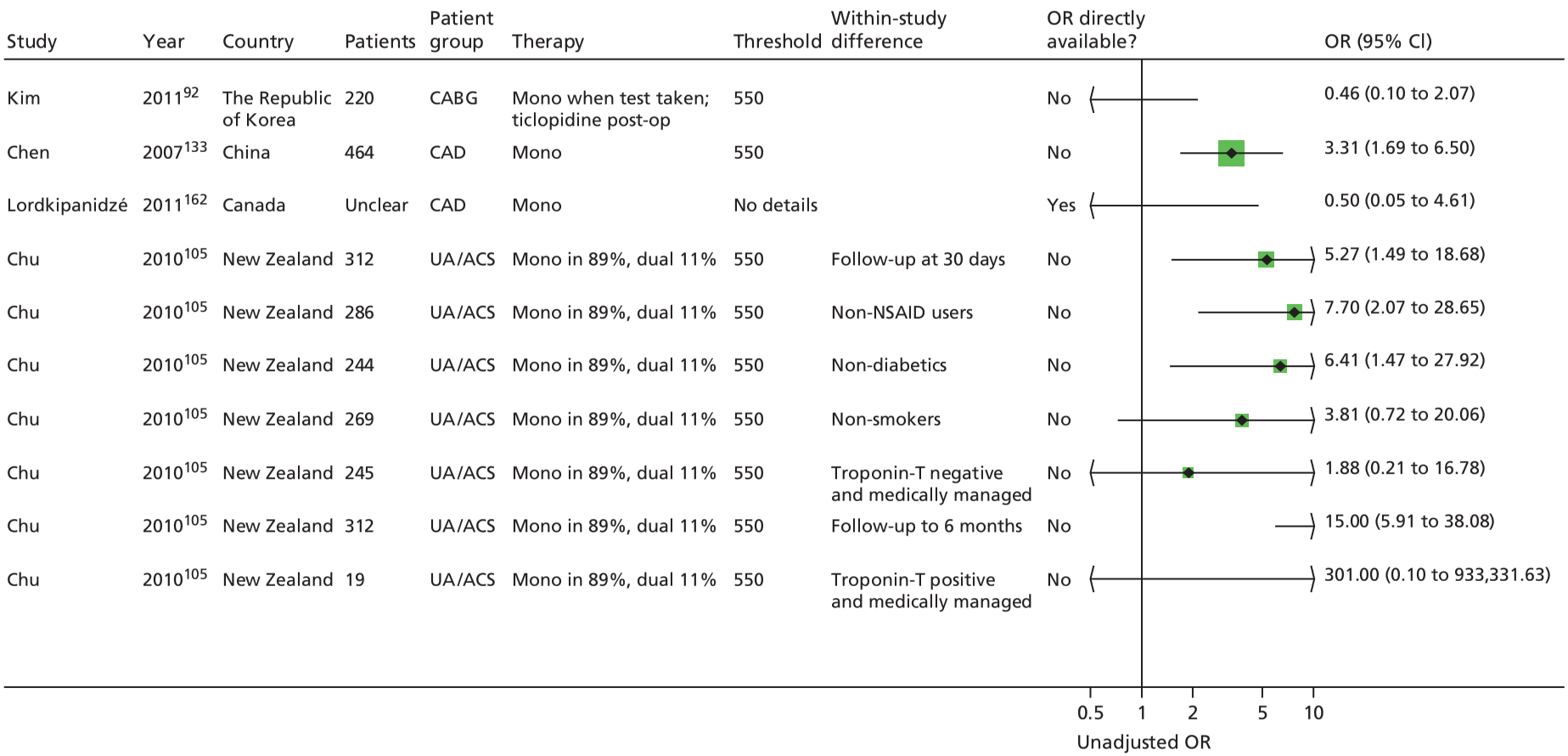

FIGURE 15 VerifyNow® Aspirin, monotherapy: MACEs, unadjusted ORs.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Chen	2007[133]	China	464	CABG	Mono	550		Yes	3.12 (1.65 to 5.90)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550		No	0.47 (0.11 to 2.04)
Chen	2007[133]	China	464	CAD	Mono	550	Cardiovascular death/ MI/stroke	Yes	1.64 (0.69 to 3.91)
Chu	2010[105]	New Zealand	19	UA/ACS	Mono in 89%, dual 11%	550	Troponin-T positive and medically managed	No	25.94 (4.72 to 142.43)
Chu	2010[105]	New Zealand	286	UA/ACS	Mono in 89%, dual 11%	550	Non-NSAID users	No	7.08 (2.07 to 24.19)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up to 6 months	Yes	10.00 (4.57 to 21.87)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up at 30 days	Yes	10.00 (4.57 to 21.87)
Chu	2010[105]	New Zealand	245	UA/ACS	Mono in 89%, dual 11%	550	Troponin-T negative and medically managed	Yes	11.20 (4.73 to 26.54)
Chu	2010[105]	New Zealand	269	UA/ACS	Mono in 89%, dual 11%	550	Non-smokers	No	3.68 (0.74 to 18.25)
Chu	2010[105]	New Zealand	244	UA/ACS	Mono in 89%, dual 11%	550	Non-diabetics	No	5.99 (1.50 to 23.93)

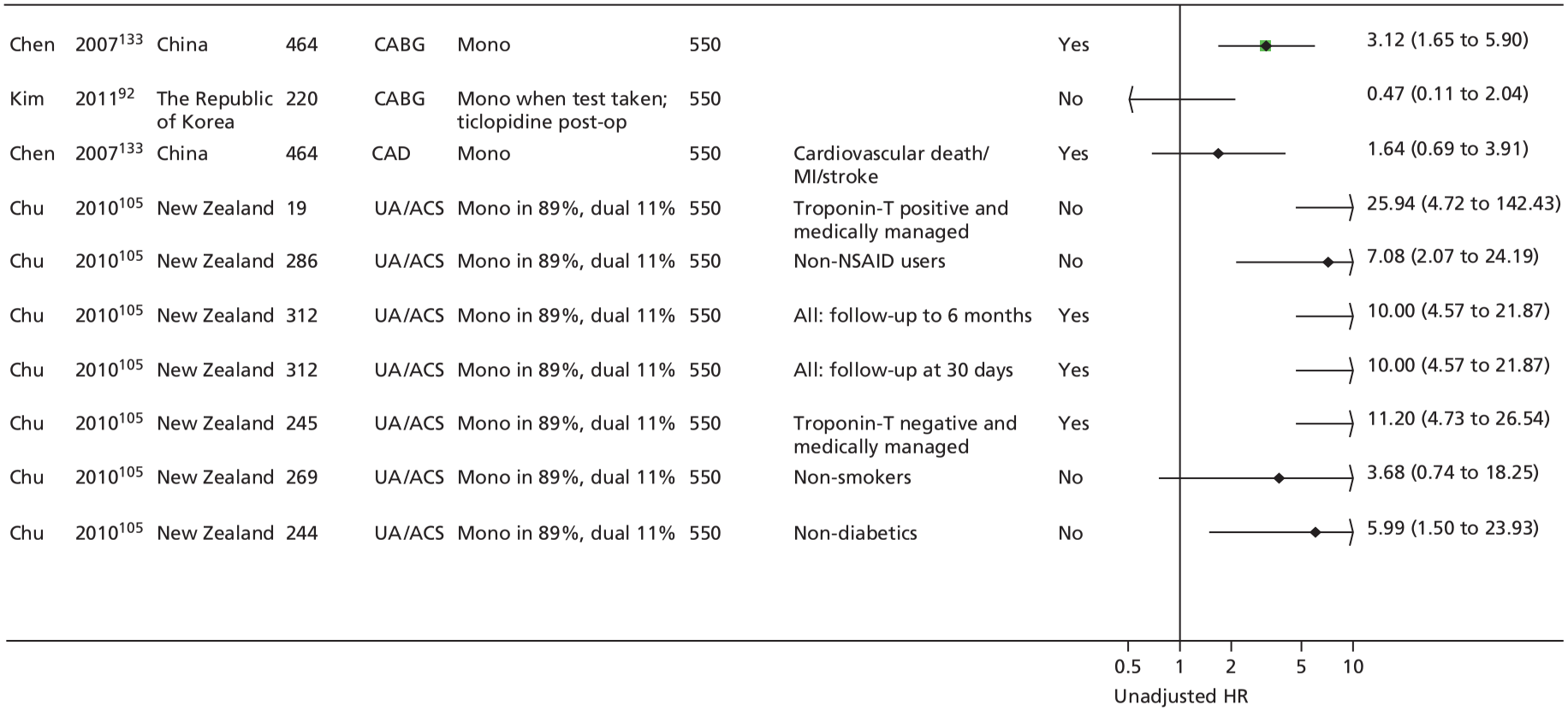

FIGURE 16 VerifyNow® Aspirin, monotherapy: MACEs, unadjusted HRs.

FIGURE 17 VerifyNow® Aspirin, monotherapy: MACEs, adjusted HRs.

Ischaemic/thrombotic events

Three studies[92,99,133] reported this outcome (*Table 24*).

Three[92,99,133] out of seven studies also reported additional ischaemic/thrombotic outcomes, and the different outcome statistics are reported in *Figures 18* and *19*. There were no statistically significant differences based on unadjusted ORs (two studies[92,99]). Two of seven unadjusted HRs were statistically significant (both based on one study[133]), with more events in the resistant group.

The study by Gluckman *et al.*[99] also reported mean [standard deviation (SD)] values of aspirin reaction units (ARUs) for groups with one or more occluded saphenous vein grafts (SVGs) versus the group with no occluded SVG, and also for patients undergoing CABG. The mean values in the group with occluded SVGs were slightly higher (indicating greater platelet reactivity), but there were no significant differences and all means were below a threshold of 550 ARUs. No adjusted statistics were reported for any studies.

Thus, there is no evidence of a greater number of events in one or the other group in the two studies with CABG populations,[92,99] while the only study[113] with the CAD population found significant differences for two outcomes.

TABLE 24 Outcome measures for reporting ischaemic/thrombotic events (VerifyNow® Aspirin, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Chen 2007[133]			✓			
Gluckman 2011[99]	✓				Mean ARU presented for groups with and without events	
Monotherapy at time of PFT, dual therapy during follow-up						
Kim 2011[92]	✓[a]		✓[a]			✓[a]

ARU, aspirin reaction unit.
a Calculated from data given in the publication.

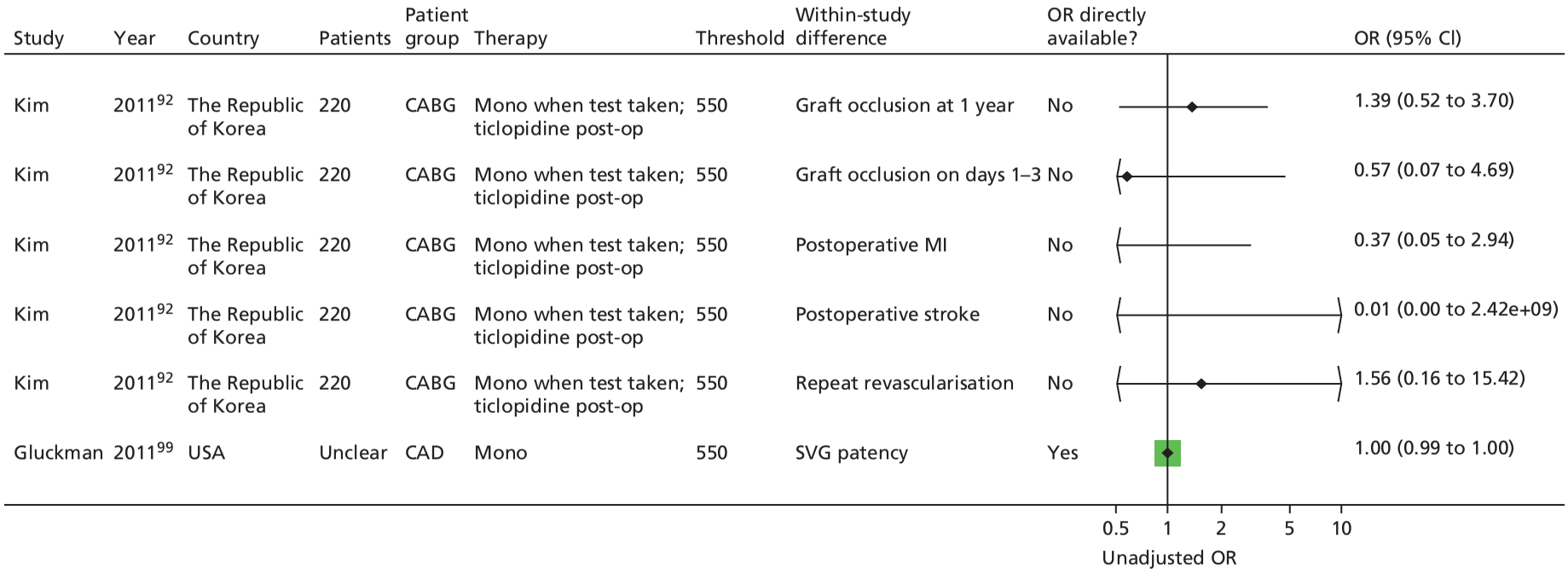

FIGURE 18 VerifyNow® Aspirin, monotherapy: ischaemic/thrombotic events, unadjusted ORs. SVG, saphenous vein graft.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Outcome	HR directly available?	HR (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion at 1 year	No	1.35 (0.55 to 3.36)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion on days 1–3	No	0.57 (0.07 to 4.59)
Chen	2007[133]	China	464	CAD	Mono	550	MI-hospitalisation for UA	Yes	3.77 (1.59 to 8.95)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative MI	No	0.38 (0.05 to 2.91)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative stroke	No	0.01 (0.00 to 2.44e+09)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Repeat revascularisation	No	1.55 (0.16 to 14.94)
Chen	2007[133]	China	464	CAD	Mono	550	Stroke/TIA	Yes	4.09 (1.15 to 14.50)

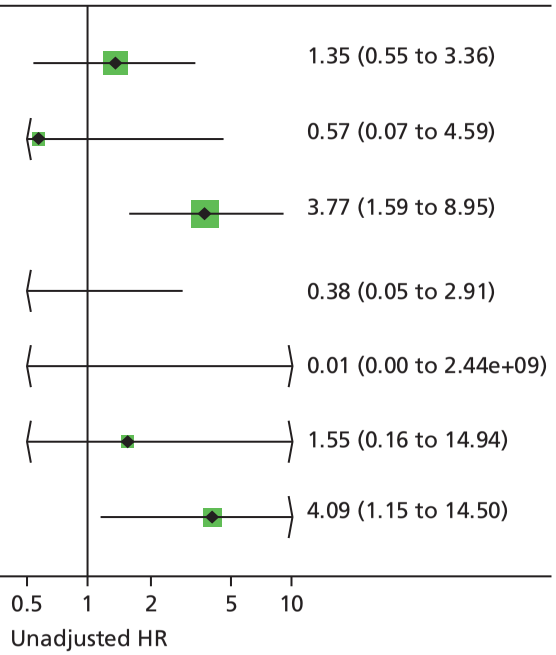

FIGURE 19 VerifyNow® Aspirin, monotherapy: ischaemic/thrombotic events, unadjusted HRs.

Bleeding events

Two studies[92,171] reported this outcome (*Table 25*).

Only two[92,171] out of seven studies reported bleeding events; these were postoperative in one study[92] and over a 4-week period in ischaemic stroke patients [randomised to aspirin and placebo or aspirin and cilostazol (Pletal®, Otsuka) in the other study].[171] The study by Kim *et al.*[92] also measured postoperative blood loss and transfused units of blood; there were no significant differences between the aspirin-resistant and sensitive groups. Too few events occurred to draw any overall conclusions: none in Lee *et al.*,[171] and two (re-exploration for bleeding) in Kim *et al.*[92] (*Figures 20* and *21*). No studies using VerifyNow® Aspirin as a PFT were identified that measured long-term adverse bleeding events.

Summary: VerifyNow® Aspirin

Seven studies[86,92,99,105,133,162,171] were identified in this category, most in stable populations, but one in patients with UA/ACS[105] and one[92] in patients with severe CAD undergoing CABG.

There was a lack of reporting of quality criteria and no study reported all details considered to be important to assess risk of bias. No study reported on blinding to patient characteristics (when undertaking the PFT). Only one study[171] gave details on the level of compliance and exclusions on the basis of this. Four[99,105,133,171] of the seven studies gave details of missing data and four[86,99,105,133] gave details of blinding of outcome assessors.

The risk of death in the resistant and sensitive groups was reported in only two studies.[86,92] In one of these,[92] only one death occurred. The other study found statistically significant results based on unadjusted and adjusted ORs, and unadjusted HR (more events in the resistant group); this was based on 43 events in 106 patients.

Major adverse cardiac events were reported in four studies.[92,105,133,162] The direction of effect was consistent across all results (more events in the resistant group). Around half of the unadjusted ORs and unadjusted HRs were statistically significant, but it should be noted that a single study[105] contributed to a large proportion of these results as several subgroup results were presented. Adjusted HRs based on two studies[105,133] were also statistically significant.

Ischaemic/thrombotic events were reported in three studies;[92,99,133] most unadjusted outcome measures were statistically non-significant, though there was a trend towards more events in resistant groups. There were no adjusted outcome measures.

Two studies[92,171] measured (short-term) bleeding events (postoperative or re-exploration for bleeding). There were only two events in total and no conclusion can be drawn from the data.

TABLE 25 Outcome measures for reporting bleeding events (VerifyNow® Aspirin, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Lee 2010[171]	✓[a]		✓[a]			0 events, therefore not calculable
Monotherapy at time of PFT, dual therapy during follow-up						
Kim 2011[92]	✓[a]		✓[a]			✓

a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Outcome	OR directly available?	OR (95% CI)
Spontaneous									
Lee	2010[171]	The Republic of Korea	119	CVD/stroke	Mono (ITT)	550	Clinical bleeding complications	No	1.00 (0.00 to 1.94e+09)
Lee	2010[171]	The Republic of Korea	102	CVD/stroke	Mono (PP)	550	Clinical bleeding complications	No	1.00 (0.00 to 3.99e+08)
Lee	2010[171]	The Republic of Korea	119	CVD/stroke	Mono (ITT)	500	Clinical bleeding complications	No	1.00 (0.00 to 1.94e+09)
Lee	2010[171]	The Republic of Korea	102	CVD/stroke	Mono (PP)	500	Clinical bleeding complications	No	1.00 (0.00 to 3.97e+08)
Post-operative									
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Re-exploration for bleeding	No	0.01 (0.00 to 3.68e+09)

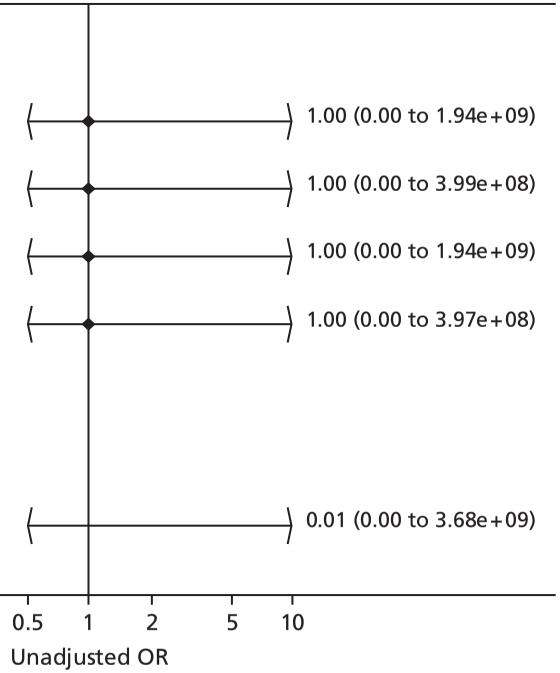

FIGURE 20 VerifyNow® Aspirin, monotherapy: bleeding events, unadjusted ORs. ITT, intention to treat; PP, per protocol.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Spontaneous									
Lee	2010[171]	The Republic of Korea	119	CVD/stroke	Mono	550	ITT	No	1.00 (0.00 to 1.93e+09)
Lee	2010[171]	The Republic of Korea	102	CVD/stroke	Mono	550	Per protocol	No	1.00 (0.00 to 3.95e+08)
Lee	2010[171]	The Republic of Korea	119	CVD/stroke	Mono	550	ITT	No	1.00 (0.00 to 1.93e+09)
Lee	2010[171]	The Republic of Korea	102	CVD/stroke	Mono	550	Per protocol	No	1.00 (0.00 to 3.95e+08)
Postoperative									
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550		No	0.01 (0.00 to 3.69e+09)

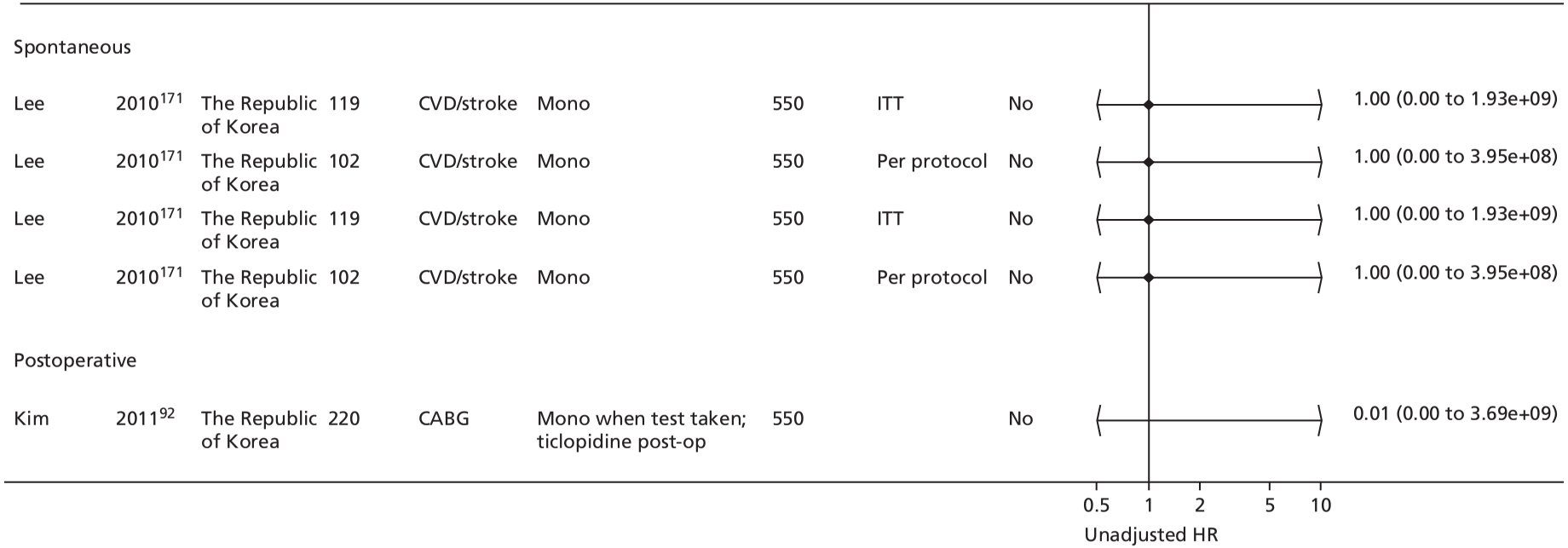

FIGURE 21 VerifyNow® Aspirin, monotherapy bleeding events, unadjusted HRs. ITT, intention to treat.

Despite the heterogeneity and lack of many statistically significant results, the direction of prognostic effect appears to be largely consistent with more events in aspirin-resistant patients (ORs and HRs usually > 1). This suggests that VerifyNow® Aspirin is a potential prognostic factor, but this is only a qualitative judgement on the evidence available; meta-analysis was not possible owing to the heterogeneity, and therefore a firm quantitative conclusion regarding whether or not VerifyNow® Aspirin is prognostic is not currently possible.

Summary: VerifyNow® Aspirin

- Seven studies used this commercial PFT.
- A lack of reporting of quality criteria hampered an overall assessment of risk of bias; only one of seven studies gave details on level of compliance.
- Heterogeneity in outcomes, patient groups and types of reported statistics meant that meta-analysis was not considered appropriate.
- Adjusted results were rarely presented, and thus the additional prognostic value of the test over other prognostic factors is difficult to ascertain.
- There was a consistent trend towards a greater number of events in the resistant groups within the studies; some of the results were statistically significant.
- Some studies contributed more results by reporting on several subgroups and not all studies contributed to all outcome measures; therefore, there are potentially some missing data and/or a bias towards certain studies (though results were not pooled).
- No studies were identified that reported on long-term bleeding events.

Thromboxane metabolite measurement

Population and test characteristics

Eleven studies[46,76,99,108,110,148,151,162,164,195,202] were identified in this category, three of which were reported in abstract form only.[162,164,202] Populations had CAD (nine studies[46,76,99,108,110,162,164,195,202]) or CVD disease/stroke (one study[148]). One study[151] included patients with various conditions including CAD, stroke, PVD and diabetes.

Most studies did not report for how long patients had had their primary underlying condition. One study[117] reported that patients had their primary underlying condition for a mean period of 41.4 months.

In nine studies[46,99,108,110,148,151,162,164,202] it appeared that patients were exclusively on monotherapy both at the time of the PFT and during follow-up. In two studies, patients were on monotherapy at the time of the PFT, and 32%[76] and 54.8%[195] of patients respectively went on to additionally receive clopidogrel at some point during follow-up. It is possible that not all studies have reported where a proportion of patients commenced additional therapies during follow-up.

Three studies measured thromboxane metabolite levels in serum/plasma[46,76,164] and nine studies measured thromboxane metabolite levels in urine.[99,108,110,148,151,162,164,195,202] Data in these groups were analysed separately.

Comedications were reported in five studies[108,148,162,164,202] and included ACE inhibitors, angiotensin II antagonists, calcium blockers, statins, beta-blockers, COX-2 antagonists, heparin, warfarin, diuretics, insulin, oral hypoglycaemics, antidepressants, anticoagulants, lipid-lowering agents and vitamin E. NSAIDs were not permitted (or had to be discontinued within a certain time period) in two studies.[108,110] One study[99] stated that 'concurrent nonsteroidal anti-inflammatory drug use did not correlate with the presence of aspirin non-responsiveness defined by this method at either time point'. In two studies, 10%[76] and 24%[195] of patients respectively were taking NSAIDs. There were no details on NSAIDs in the remaining studies.

The number of participants in the studies ranged from 61 to 3261 (see *Table 26*). Where reported, average ages of patients ranged from 53 years (mean value) to 69 years (median value), with most average ages around the early 60s. There were more men than women in the eight studies that reported this[46,76,99,108,110,148,151,195] (the remaining three studies[162,164,202] did not report details), with proportions of men ranging from 59% to 90%. The proportion of patients with diabetes ranged from 19% to 48%, and that of smokers from 16.6% to 71% (where reported, see *Table 26*). All studies were conducted in hospital settings.

The dose of aspirin ranged between 75 mg/day and 325 mg/day, with the exception of one study,[148] where the dose was high at 650 mg/day. This study included patients with a non-cardioembolic, non-incapacitating cerebral infarction. There were no details on dose in one study.[151] Details were variable across studies regarding the length of time patients had been receiving aspirin therapy, with some noting a minimum period and some giving no details (see *Table 26*). Two studies stated aspirin was provided in enteric or plain form[99,110] and no other studies provided this information.

The main study characteristics are listed in *Table 26*. Note that in some studies baseline characteristics have been reported only according to groups with/without adverse clinical events, or groups with occluded or patent SVG during CABG surgery, rather than for the total study population.

Most studies reported no details on the timing of the PFT after aspirin ingestion. One study[148] stated that there were up to 24 hours between aspirin dose and PFT. *Table 27* shows details of test characteristics.

Study design and quality

Results of the risk-of-bias assessment can be found in *Tables 28–31*.

Patient selection was independent of study outcome in 10 of the included studies,[46,76,99,108,110,148,162,164,195,202] with the PFT preceding any outcomes (as specified in the study selection criteria). One study[151] used a case–control design, so patient selection was not independent of outcome, but the taking of samples for the PFT still preceded the outcomes and so this study was included. Five of 11 studies stated that consecutive patients were enrolled into the study.[46,76,108,110,164] Details on posteligibility exclusion of patients were provided in five studies;[46,76,99,148,151] reasons included compliance with aspirin treatment at each follow-up visit,[151] patients in whom the outcome was not assessed[99] or no provision of urine sample.[148]

A predefined threshold was stated in only three studies[46,99,202] and this was not consistent across the studies (cut-offs of 298 pg/mg creatinine,[202] 400 pg/mg creatinine[99] and 5 nmol/10^{11} platelets[46]). The remaining studies used tertiles,[108] quartiles,[195] median value,[110] derived the value by receiver operating characteristic (ROC) analysis,[76] presented mean values for groups with and without events[148,151] or gave no details.[162,164] Three studies[108,151,195] gave clear details of blinding of laboratory staff to patient characteristics.

Outcome measures of interest were clearly predefined in all studies, and five studies[76,99,108,148,151] had details of blinded assessment of outcomes. Five studies appeared to have no loss to follow-up[46,108,148,151,195] and there were no details in three studies.[162,164,202] In the remaining three studies the loss to follow-up was 4%,[99] 17%[110] and 19%.[76]

Compliance was assessed in six studies.[46,99,108,151,164,195] Methods included interview, plasma concentration of salicylates and pill counts. In one study,[46] patients who stated that they were not taking the prescribed aspirin were included as a separate subgroup in the analysis (resistant and non-compliant). Another study[76] did not exclude patients as 'resistance cannot be distinguished from non-compliance'.

Three studies[76,148,151] undertook adjusted analyses, with some overlap between the adjustment factors where stated.

TABLE 26 Population characteristics (thromboxane metabolite measurement, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Serum/plasma and urinary *Monotherapy at time of PFT and during follow-up*										
Miyata 2011,[164] Japan (abstract)	592 (583 eligible for analyses)	No details	Mono	CAD	No details	No	Some higher doses (> 100 mg/day), some lower doses (≤ 100 mg/day)	No details	No details	No details
Serum/plasma (metabolite used: TxB_2) *Monotherapy at time of PFT and during follow-up*										
Cotter 2004,[46] Israel	73 (61 eligible for analyses)	Mean 53 (SD 8)	Mono	CAD	Smokers: 23% Diabetes: 19%	No	100 mg/day	At least 1 month	14.8	5 nmol/10^{11} platelets (lowest TxB_2 production observed in healthy volunteers)
Frelinger 2009,[76] USA	700 (555 eligible for analyses)	Mean 60.7 (SEM 0.44)	Mono (32% dual during follow-up)	CAD	Smokers: 22% current smokers (72% prior smokers) Diabetes: 27%	No	81 or 325 mg/day	At least 3 days	8.1	Resistant if ≤ 3.1 ng/ml

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Urinary (metabolite used: 11-dehydro-TxB_2)										
Monotherapy at time of PFT and during follow-up										
Addad 2010,[108] Tunisia	204	Mean 59 (SD 10)	Mono	CAD	Smokers: $n = 145$ (71%) Diabetes: $n = 79$ (38.7%)	No	250 mg/day	At least 2 months on enrolment	No details	No details
Bruno 2004,[148] USA	61 (83 in total because 22 patients on ticlopidine; demographics based on 61 patients)	Mean 61 (SD 11)	Mono	CVD/stroke	Smokers: $n = 37$ (45%) Diabetes: $n = 40$ (48%)	No	650 mg/day	At least 7 days	No details	No details
Eikelboom 2002,[151] Australia	488 (976 enrolled: 488 cases, 488 controls)	Mean 67.3 (SD 7.2)	Mono	Miscellaneous	Smokers: $n = 81$ (16.6%) Diabetes: $n = 159$ (32.6%)	No	No details	No details	No details	No details

continued

TABLE 26 Population characteristics (thromboxane metabolite measurement, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Eikelboom 2008,[195] Australia	3261	With an event (stroke, MI or cardiovascular death; *n* = 144): median 69 Without an event (*n* = 3117): median 64	Mono (54.8% dual during follow-up)	CAD	*Current smokers:* With an event: *n* = 26 (18.1%) Without an event: *n* = 632 (20.3%) *Former smokers:* With an event: *n* = 76 (52.8%) Without an event: *n* = 1547 (49.6%) *Diabetes:* With an event: *n* = 73 (50.7%) Without an event: *n* = 1381 (44.3%)	No	81 mg/day (median) Range 75–162 mg/day	At least one month	No details	No details

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Eskandarian 2011,[202] Iran (abstract)	124	No details	Mono	CAD	No details	No	80 mg/day	At least 7 days before test	65.3	Resistant if > 298 pg/mg Intermediate response 134–298 pg/mg Sensitive if < 134 pg/mg
Gluckman 2011,[99] USA	229	For patients with ≥ 1 occluded SVG ($n = 70$): mean 63 (range 55–72) For patients with patent SVG ($n = 159$): mean 63 (range 57–71)	Mono	CAD	Smokers: $n = 52$ (22.7%) Diabetes: $n = 84$ (36.7%)	Yes: CABG	325 mg/day	No details	No details	Aspirin responsive if TxB_2 < 400 pg/mg creatinine
Lordkipanidzé 2011,[162] UK (abstract)	198	No details	Mono	CAD	No details	No	80–325 mg/day	No details	No details	No details
Thomson 2009,[110] India	63	Mean 57 (SD 10)	Mono	CAD	Smokers: $n = 43$ (73%) Diabetes: $n = 22$ (34.9%)	No	75 mg/day	At least 7 days	38.1	Aspirin resistance defined as normalised urinary TxB_2 level ≥ 67.9 ng/mmol creatinine

SEM, standard error of the mean.

TABLE 27 Test characteristics (thromboxane metabolite measurement, monotherapy)

Study	Details of kit/manufacturer	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Serum/plasma and urinary *Monotherapy at time of PFT and during follow-up*				
Miyata 2011,[164] (abstract)	Serum TxB_2 Urinary 11-dehydro-TxB_2	No details	Serum TxB_2 Urinary 11-dehydro-TxB_2	No details
Serum *Monotherapy at time of PFT and during follow-up*				
Cotter 2004[46]	TxB_2 plasma (enzyme immunoassay kit obtained from Amersham, Buckinghamshire, UK)	No details	Collagen (1 µmol)	Aspirin administered on enrolment
Frelinger 2009[76]	Serum TxB_2	No details	No details	No details
Urinary *Monotherapy at time of PFT and during follow-up*				
Addad 2010[108]	Urinary 11-dehydro-TxB_2	Enzyme-linked immunoassay	Enzyme-linked immunoassay	No details
Bruno 2004[148]	Urinary 11-dehydro-TxB_2	No details	No details	Up to 24 hours
Eikelboom 2002[151]	Urinary 11-dehydro-TxB_2	Enzyme immunoassay (Cayman Chemical, Ann Arbor, MI, USA)	Enzyme immunoassay (Cayman Chemical, Ann Arbor, MI, USA)	No details
Eikelboom 2008[195]	Urinary 11-dehydro-TxB_2	No details	No details	No details
Eskandarian 2011[202]	Urinary 11-dehydro-TxB_2	No details	No details	No details
Gluckman 2011[99]	Urinary 11-dehydro-TxB_2	No details	No details	No details
Lordkipanidzé 2011[162] (abstract)	Urinary 11-dehydro-TxB_2	No details	No details	No details
Thomson 2009[110]	Urinary 11-dehydro-TxB_2	No details	No details	No details

TABLE 28 Risk of bias, patient selection (thromboxane metabolite measurement, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Serum/plasma and urinary			
Miyata 2011[164] (abstract)	Consecutive	Yes	No details
Serum/plasma			
Cotter 2004[46]	Consecutive	Yes	76/82 potentially eligible patients agreed to be interviewed; 73/76 who were on aspirin for at least 1 month were enrolled
Frelinger 2009[76]	Consecutive	Yes	Stated that less than 3% of eligible patients declined participation (reason not given)
Urinary			
Addad 2010[108]	Consecutive	Yes	No details
Bruno 2004[148]	Unclear: consecutive patients screened for participation in the trial	Yes	98 patients initially gave signed consent; 8/98 withdrew consent and 7/98 did not provide a urine sample
Eikelboom 2002[151]	Control subjects randomly selected	No	9541 patients in HOPE study; 9282 provided urine samples, samples from 5529 (Canadian centres only) sent to laboratory. Of those, only those who were taking aspirin before and at randomisation, and at each follow-up visit, were eligible for inclusion (number not stated). 488 cases and controls selected from the eligible/included
Eikelboom 2008[195]	Unclear (patients who complied with a request to provide a sample)	Yes	No details
Eskandarian 2011[202] (abstract)	No details	Yes	No details
Gluckman 2011[99]	No details	Yes	Patients for whom SVG patency not assessed or those not on aspirin monotherapy. Authors stated that the study population was representative of patients undergoing isolated CABG surgery based on comparison with the Society of Thoracic Surgeons National Database
Lordkipanidzé 2011[162] (abstract)	No details	Yes	No details
Thomson 2012[110]	Consecutive	Yes	No details

HOPE, Heart Outcomes Prevention Evaluation.

TABLE 29 Risk of bias, PFT (thromboxane metabolite measurement, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Serum/plasma and urinary			
Miyata 2011[164] (abstract)	No details	No details	No details
Serum/plasma			
Cotter 2004[46]	Yes (5 nmol/10^{11} platelets)	Patients classified as nonresponsive: results in the range observed in volunteers not taking aspirin Patients classified as responsive: results in ranges that are observed in takers Cut-off: lowest TxB_2 production value that was observed in non-takers	No details
Frelinger 2009[76]	No (ROC analysis)	ROC analysis of serum TxB_2 levels in current study with regard to MACE (resistant if $\leq$ 3.1 ng/ml)	No details
Urinary			
Addad 2010[108]	No (tertiles)	Tertiles	Yes; stated that all assays were performed in a blinded manner
Bruno 2004[148]	No (median values for patients with and without events presented)	N/A	Possible; no details, but laboratory off-site
Eikelboom 2002[151]	No (mean/median values for patients with and without events presented)	N/A	Assays were performed by laboratory staff blinded to patient status (case or control) and also assayed in random order
Eikelboom 2008[195]	No (quartiles)	Quartiles	Yes; 'Laboratory staff performing the assays were blinded to treatment allocation and to whether the patients had experienced a primary event'
Eskandarian 2011[202] (abstract)	Yes (three groups: resistant > 298 pg/mg, intermediate response 134–298 pg/mg, sensitive < 134 pg/mg)	No details	No details
Gluckman 2011[99]	Yes (aspirin responsive if < 400 pg/mg creatinine; but a threshold of 450 pg/mg creatinine used in model)	'According to established criteria' (reference cited[221])	No details
Lordkipanidzé 2011[162] (abstract)	No details	No details	No details
Thomson 2012[110]	No (population median value)	Median value of absolute urinary 11-dehydro-TxB_2 level of 320 pg/ml used as cut-off in relation to clinical outcomes	No details

N/A, not applicable; ROC, receiver operating characteristic.

TABLE 30 Risk of bias, outcomes and study attrition (thromboxane metabolite measurement, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Serum/plasma and urinary			
Miyata 2011[164] (abstract)	Yes	No details	No details
Serum/plasma			
Cotter 2004[46]	Yes	No details	Appears that there was no loss to follow-up
Frelinger 2009[76]	Yes	Yes; all clinical outcome data obtained by research personnel blinded to results of PFTs	127/682 lost to follow-up (for MACE outcome)
Urinary			
Addad 2010[108]	Yes	Yes; follow-up clinicians were blinded to PFT results	Stated that none of the included patients was lost to follow-up
Bruno 2004[148]	Yes	Yes; assay results not revealed to investigators until after follow-up examinations and vascular event determinations	Appears that there was no loss to follow-up
Eikelboom 2002[151]	Yes	Yes (outcome occurred before analysis of sample)	None; retrospective [patients who had a confirmed event were defined as cases and controls were randomly selected from among those with no events (sex and age matched)]
Eikelboom 2008[195]	Yes	No details	Appears that there was no loss to follow-up
Eskandarian 2011[202] (abstract)	Yes	No details	No details
Gluckman 2011[99]	Yes	Yes; stated that images were analysed by two blinded reviewers (98% concordance) with a third reviewer adjudicating as necessary	10/229 not included at 6 months
Lordkipanidzé 2011[162] (abstract)	Yes	No details	No details
Thomson 2012[110]	Yes	No details	11/63 lost to follow-up, unclear if excluded from analysis

TABLE 31 Risk of bias, confounders (thromboxane metabolite measurement, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Serum/plasma and urinary						
Miyata 2011[164] (abstract)	Design: N/A Analysis: appears that adjustment for possible confounders was undertaken, but no adjusted measures presented	No details	N/A	Yes	Interview and by checking plasma concentration of salicylic acid	No details
Serum/plasma						
Cotter 2004[46]	Design: N/A Analysis: no	N/A	N/A	Yes	Interview and corroboration with another adult (usually spouse)	12/21 patients (out of a total of 73) whose response was classified as non-responsive stated that they were not taking the medication, the other nine claimed they were
Frelinger 2009[76]	Design: N/A Analysis: yes (OR, HR)	Sex, BMI, TIMI score, aspirin dose, platelet count, use of clopidogrel, statins or oral hypoglycaemic agents	Yes (the assumption of proportionality was tested and found to be valid)	Not specifically	By TxB_2 levels	'Two patients had serum TxB_2 levels in the range observed for aspirin-free healthy controls, and their platelet function was therefore consistent with aspirin noncompliance. Because "resistance" cannot be distinguished from noncompliance, these subjects were not excluded from follow-up'

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Urinary						
Addad 2010[108]	Design: N/A Analysis: no	N/A	N/A	Yes	Interview at study enrolment and during follow-up period	No details
Bruno 2004[148]	Design: N/A Analysis: yes (HR)	Age, sex, hypertension, diabetes, smoking, ischaemic heart disease, prior stroke, hypercholesterolaemia, mean 11-dehydro-TxB_2 level	No details	No details	N/A	N/A
Eikelboom 2002[151]	Design: N/A Analysis: yes (OR)	Included conventional vascular risk factors, co-interventions and randomised treatment allocation (full details not given)	N/A	Yes	Assessed compliance with aspirin therapy at each follow-up visit and only considered for inclusion patients who were taking aspirin before randomisation and at 6-month follow-up visits. Patients who discontinued aspirin at any time during the study were not included	No details

continued

TABLE 31 Risk of bias, confounders (thromboxane metabolite measurement, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Eikelboom 2008[195]	Design: N/A Analysis: yes (HR)	Subsets of (depending on model): age, sex, BMI, current smoking, hypertension, hypercholesterolaemia, diabetes, past history of MI, stroke, TIA, peripheral artery disease, PCI, CABG, endarterectomy, peripheral angioplasty/ bypass, aspirin dose, study clopidogrel, NSAIDs, statins, beta-blockers, diuretics, calcium channel blockers, ACE inhibitors, other blood pressure-lowering agents, oral hypoglycaemic agents, insulin, time of urine collection	No details	Yes	The use of medications, including aspirin dose, was recorded at each follow-up	States in the discussion that non-compliance with aspirin therapy could account for variability in thromboxane concentrations, but that 'the present data show that factors not related to compliance with aspirin therapy, including age and sex, as well as use of several concomitant therapies, independently determine urinary 11-dehydro thromboxane B_2 concentrations'

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Eskandarian 2011[202] (abstract)	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Gluckman 2011[99]	Design: N/A Analysis: no	N/A	N/A	Yes	Pill counts at each postoperative encounter	No details
Lordkipanidzé 2011[162] (abstract)	Design: N/A Analysis: unclear whether adjusted or unadjusted OR	No details	N/A	No details	N/A	N/A
Thomson 2012[110]	Design: N/A Analysis: no	N/A	N/A	No; 'Aspirin therapy was not supervised and compliance was not verified by assaying'	N/A	N/A

BMI, body mass index; N/A, not applicable; TIMI, thrombolysis in myocardial infarction.

Overview of outcomes

Eleven studies were identified; three of these[46,76,164] undertook thromboxane measurement in serum/plasma, and nine studies[99,108,110,148,151,162,164,195,202] measured thromboxane in urine (one study[164] in both categories) (*Table 32*).

Death

Death was reported in only 3[76,151,195] of 11 studies (*Table 33*). Outcome statistics are shown in *Figures 22–25*. Unadjusted ORs and HRs were calculable from Frelinger *et al.*[76] (measurement in serum/plasma), all of which showed a trend towards more events in the resistant arm, though none were statistically significant. The other two studies (measurement in urine) reported adjusted ORs[151] and adjusted HRs.[195] Again, all reflected a greater number of events in the resistant arm; two of the adjusted ORs were statistically significant. Note that this is based on comparison of different quartiles rather than using a single cut-off. Overall, the trend was consistent (more events in the resistant arm), but based on few studies.

TABLE 32 Outcomes (thromboxane metabolite measurement, monotherapy)

Study	Death	MACE	Ischaemic/ thrombotic	Bleeding	Length of follow-up
Serum/plasma and urinary					
Miyata 2011[164] (abstract)		✓			2 years
Serum/plasma					
Cotter 2004[46]		✓	✓		12 months
Frelinger 2009[76]	✓	✓			Mean 24.8 (SD 0.3) months
Urinary					
Addad 2010[108]		✓			1 year
Bruno 2004[148]			✓		Mean 2 months (no SD)
Eikelboom 2002[151]	✓	✓	✓		5 years
Eikelboom 2008[195]	✓	✓	✓	✓	Median 28 months (no SD)
Eskandarian 2011[202] (abstract)		✓			1 year
Gluckman 2011[99]			✓		6 months
Lordkipanidzé 2011[162] (abstract)		✓			3 years
Thomson 2012[110]		✓			Median 36 (range 1–53) months

TABLE 33 Outcome measures for reporting death (thromboxane metabolite measurement, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Serum/plasma						
Frelinger 2009[76]	✓[a]		✓[a]			✓[a]
Urinary						
Eikelboom 2002[151]		✓				
Eikelboom 2008[195]				✓		

a Calculated from data given in the publication.

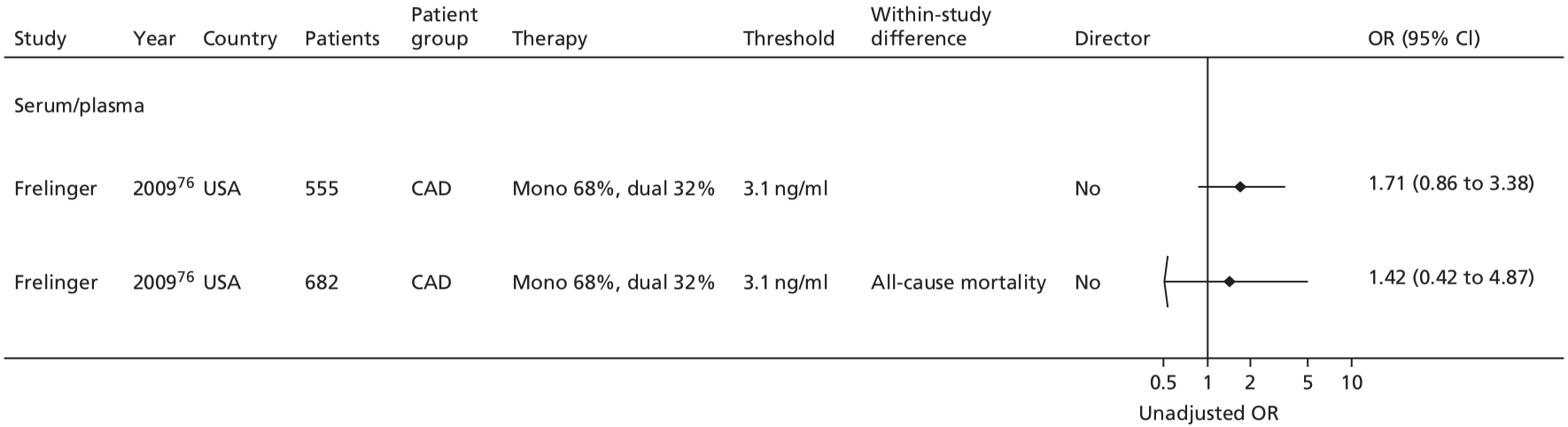

FIGURE 22 Thromboxane, monotherapy: death, unadjusted ORs.

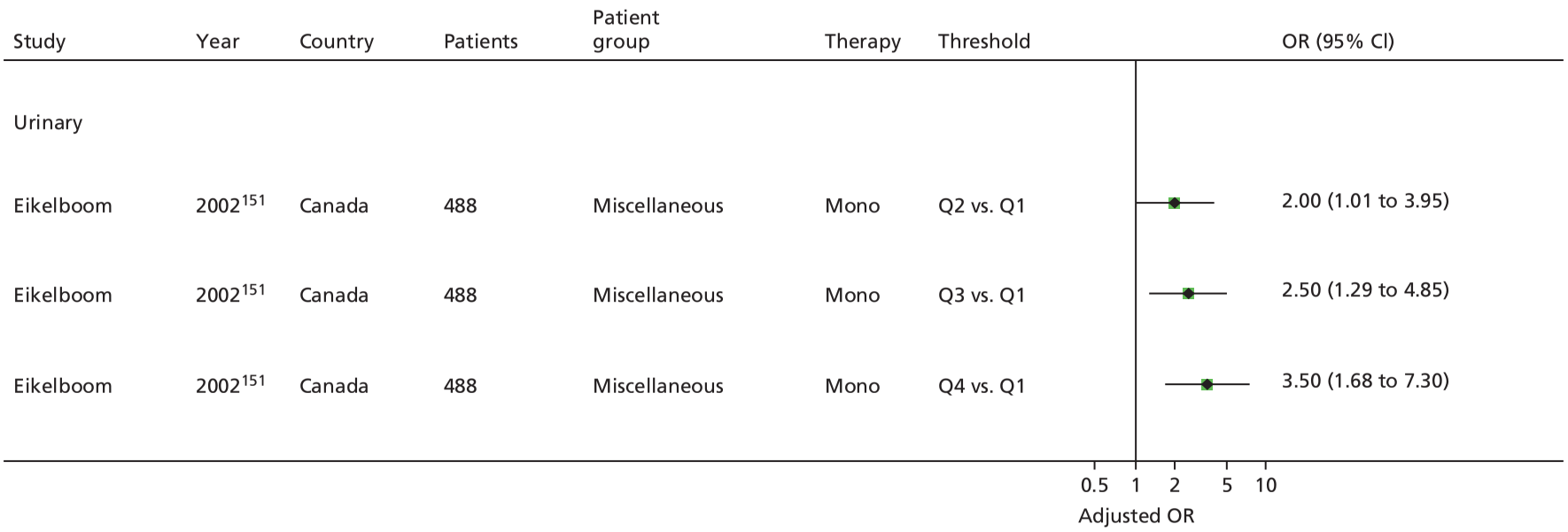

FIGURE 23 Thromboxane metabolite measurement, monotherapy: death, adjusted ORs. Q, quartile.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Serum/plasma									
Frelinger	2009[76]	USA	682	CAD	Mono 68%, dual 32%	3.1 ng/ml	All-cause mortality	No	1.41 (0.43 to 4.66)
Frelinger	2009[76]	USA	660	CAD	Mono 68%, dual 32%	3.1 ng/ml	Cardiovascular mortality	No	4.85 (0.94 to 25.01)

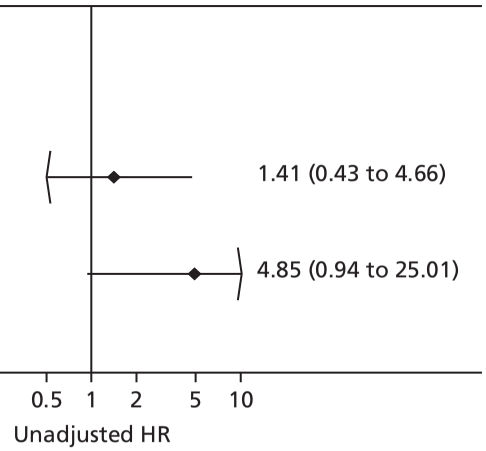

FIGURE 24 Thromboxane metabolite measurement, monotherapy: death, unadjusted HRs.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR (95% CI)
Urinary								
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Cardiovascular death	2.16 (0.97 to 4.82)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Cardiovascular death (different definition of baseline time zero)	2.59 (0.91 to 7.40)

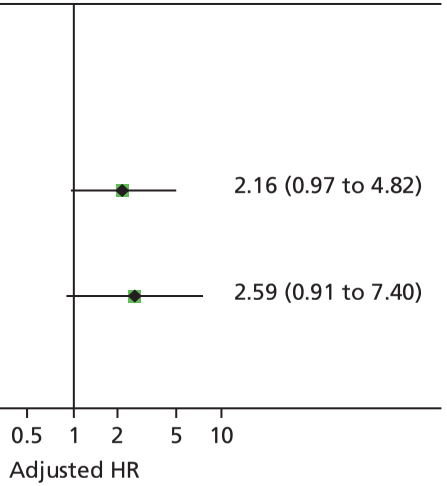

FIGURE 25 Thromboxane metabolite measurement, monotherapy: death, adjusted HRs. Q, quartile.

Major adverse cardiac events

Major adverse cardiac events were reported in nine studies (*Table 34*).[46,76,108,110,151,162,164,195,202] Outcome statistics are shown in *Figures 26–29*. For two studies,[110,164] results could not be presented in forest plots: one[164] stated that 'no ex vivo measurements for residual platelet functions and COX activities were associated with cardiovascular events. Residual platelet functions correlated poorly with residual COX activities, and were inconsistent with assessments made 6 months later.' The other[110] found that a greater number of MACEs occurred in the upper two quartiles (higher urinary thromboxane levels) than in the lower two and that this difference was statistically significant ($p = 0.04$); however, the difference was not present when normalised levels of urinary thromboxane were considered.

Eight unadjusted ORs were presented, based on four studies, three measuring thromboxane in urine[108,162,202] and one in serum/plasma.[76] Six of the ORs reflected more events occurring in the resistant arm, but only two were statistically significant. Four adjusted ORs were presented, based on two studies.[76,151] The direction of effect was consistent and two were statistically significant (more events in the resistant arm).

There were 10 unadjusted HRs based on four studies.[76,108,195,202] Although overall results showed that there were more events in the resistant group, including the three statistically significant results, the direction of effect is not consistent within two studies contributing three[195] and four[108] unadjusted HRs each; this reflects the effect of using different cut-offs (in this case comparison of different tertiles or quartiles).

TABLE 34 Outcome measures for reporting MACEs (thromboxane, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Serum/plasma and urinary						
Miyata 2011[164] (abstract)					Narrative description of results only	
Serum/plasma						
Cotter 2004[46]						✓[a]
Frelinger 2009[76]	✓[a]	✓	✓[a]	✓		✓[a]
Urinary						
Addad 2010[108]	✓[a]		✓[a]			✓[a]
Eikelboom 2002[151]		✓				
Eikelboom 2008[195]			✓	✓		
Eskandarian 2011[202] (abstract)	✓[a]		✓[a]			✓[a]
Lordkipanidzé 2011[162] (abstract)	✓					
Thomson 2012[110]					Raw data not presented (only a *p*-value)	

a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Director	OR (95% CI)
Serum/plasma									
Frelinger	2009[76]	USA	660	CAD	Mono 68%, dual 32%	3.1 ng/ml	Cardiovascular mortality	No	4.93 (0.93 to 26.07)
Urinary									
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (RAVE)	No	1.56 (0.31 to 7.93)
Addad	2010[08]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (MACE)	No	1.78 (0.70 to 4.52)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (RAVE)	No	6.64 (1.30 to 33.84)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (MACE)	No	0.74 (0.29 to 1.92)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High or intermediate vs. low	No	1.36 (0.61 to 3.06)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High vs. intermediate or low	No	2.22 (1.03 to 4.81)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	No details		Yes	0.35 (0.10 to 1.26)

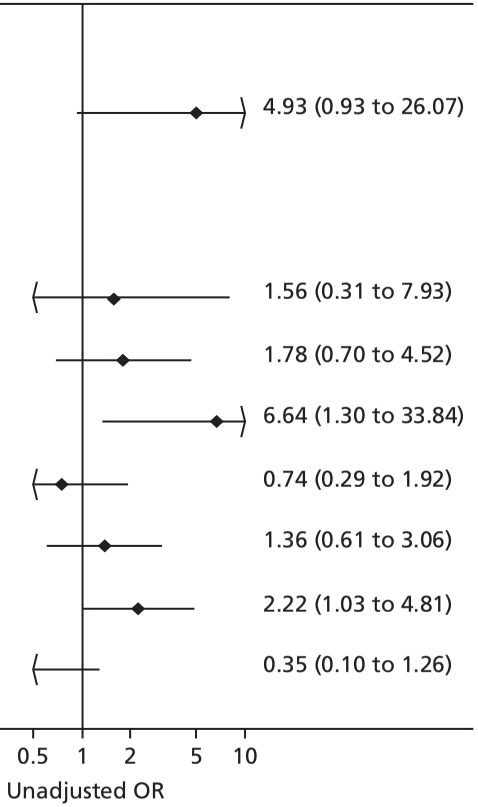

FIGURE 26 Thromboxane metabolite measurement, monotherapy: MACEs, unadjusted ORs. RAVE, recurrent acute vascular event.

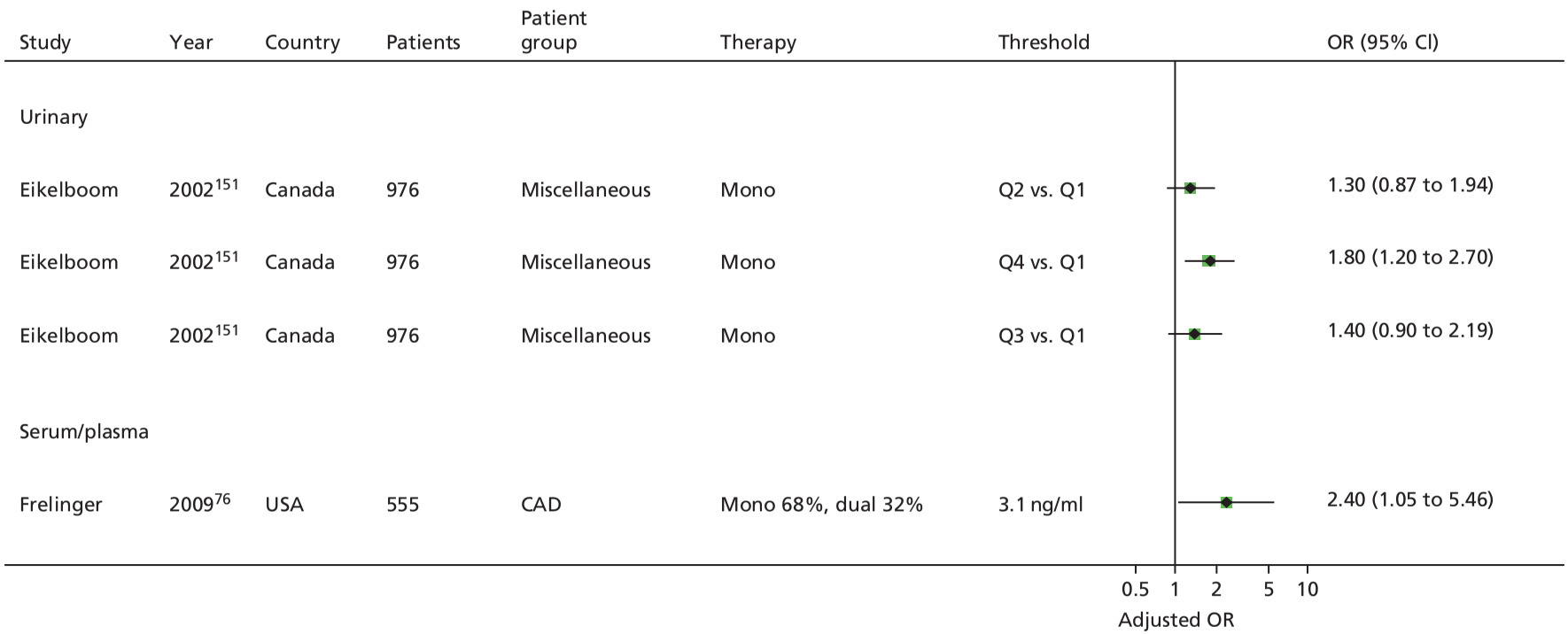

FIGURE 27 Thromboxane metabolite measurement, monotherapy: MACEs, adjusted ORs. Q, quartile.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Serum/plasma									
Frelinger	2009[76]	USA	555	CAD	Mono 68%, dual 32%	3.1 ng/ml	MACE	No	1.60 (0.90 to 2.85)
Urinary									
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (RAVE)	No	6.38 (1.29 to 31.61)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (MACE)	No	1.72 (0.71 to 4.16)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (RAVE)	No	0.76 (0.31 to 1.85)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (MACE)	No	1.55 (0.31 to 7.66)
Eikelboom	2010[195]	12 countries	3261	CAD	Mono or dual	Quartiles	Quartile 4 vs. tertile 1	Yes	1.84 (1.19 to 2.84)
Eikelboom	2010[195]	12 countries	3261	CAD	Mono or dual	Quartiles	Quartile 2 vs. tertile 1	Yes	0.81 (0.48 to 1.36)
Eikelboom	2010[195]	12 countries	3261	CAD	Mono or dual	Quartiles	Quartile 3 vs. tertile 1	Yes	0.92 (0.56 to 1.52)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High or medium vs. low	No	1.30 (0.66 to 2.55)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High vs. medium or low	No	1.94 (1.02 to 3.68)

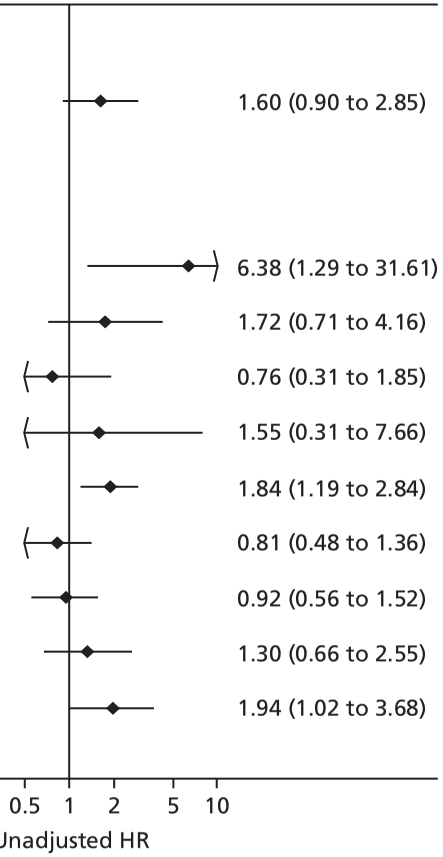

FIGURE 28 Thromboxane metabolite measurement, monotherapy: MACEs, unadjusted HRs. RAVE, recurrent acute vascular event.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	HR (95% CI)
Urinary								
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Model 1	1.71 (1.10 to 2.65)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q3 vs. Q1	Model 1	0.87 (0.52 to 1.45)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q2 vs. Q1	Model 1	0.78 (0.46 to 1.32)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Model 2	1.55 (0.99 to 2.42)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q3 vs. Q1	Model 2	0.78 (0.47 to 1.30)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q2 vs. Q1	Model 2	0.79 (0.44 to 1.42)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Model 3	1.66 (1.06 to 2.60)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q3 vs. Q1	Model 3	0.78 (0.46 to 1.31)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q2 vs. Q1	Model 3	0.83 (0.49 to 1.40)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Time zero when urine collected	1.57 (0.87 to 2.84)
Eikelboom	2008[195]	12 countries	3261	CAD	Mono or dual	Q4 vs. Q1	Excluded those with event before urine taken	1.51 (0.95 to 2.40)
Serum/plasma								
Frelinger	2009[76]	USA	555	CAD	Mono 68%, dual 32%	3.1 ng/ml		2.22 (1.21 to 4.09)

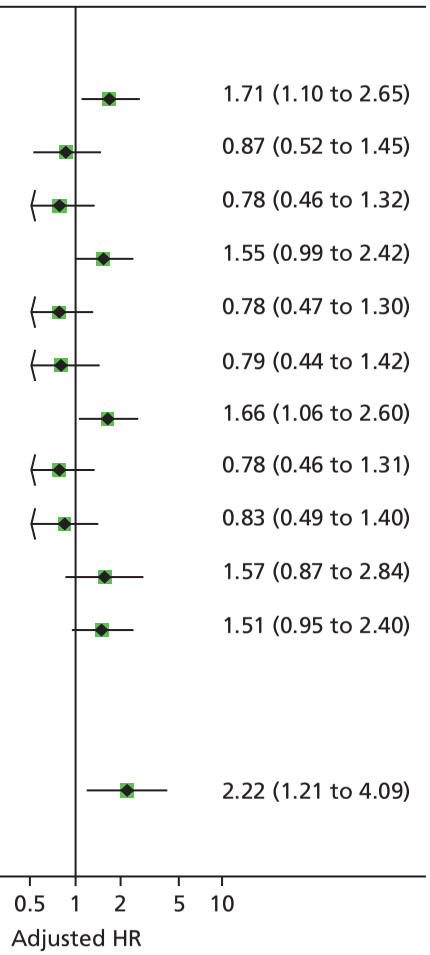

FIGURE 29 Thromboxane metabolite measurement, monotherapy: MACEs, adjusted HRs. Q, quartile.

There were 12 adjusted HRs based on two studies,[76,195] with 11 being based on only one study,[195] reflecting the use of different models (adjustment factors) and the comparison of different quartiles rather than one cut-off. One study (serum/plasma)[76] showed a statistically significant result (more events in the resistant group), whereas the direction of effect was evenly split in the study generating 11 outcome statistics.

Overall, there is a trend towards more MACEs in the resistant arm, but there is some uncertainty due to the relatively small number of studies contributing MACE results and the fact that there is some inconsistency within studies (depending on thresholds used). Only one study[76] measuring thromboxane in serum/plasma was represented in the forest plots. It was therefore not possible to compare results between the two methods, though the direction of effect (more events in the resistant group) was consistent with the majority of results.

Ischaemic/thrombotic events

This outcome measure was reported in five studies (*Table 35*).[46,99,148,151,195] Outcome statistics are presented in *Figures 30–33*. Data from one study[148] could not be represented in the forest plots. There was no significant difference in thromboxane levels in those with and without a vascular event.

Unadjusted and adjusted ORs (based on three studies[46,99,151]) showed a consistent direction of effect (more events in the resistant group), with the exception of two of six results from one study (Eikelboom,[151] adjusted ORs). All four unadjusted ORs and three of the eight adjusted ORs were statistically significant.

Two unadjusted HRs (based on one study[46]) were statistically significant (more events in the resistant groups), as was one of two adjusted HRs (based on a different study[195]).

Overall, the direction of effect is consistent (more events in the resistant group), but based on few studies. Note that one study[151] contributes to six of eight adjusted ORs, and that the direction of effect is not consistent within this study (reflecting different outcomes and thresholds).

TABLE 35 Outcome measures for reporting ischaemic/thrombotic events (thromboxane metabolite measurement, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Serum/plasma						
Cotter 2004[46]	✓[a]		✓[a]			✓[a]
Urinary						
Bruno 2004[148]					Median thromboxane levels compared in those with and without an event	
Eikelboom 2002[151]		✓				
Eikelboom 2008[195]				✓		
Gluckman 2011[99]	✓	✓				

a Calculated from data given in the publication.

FIGURE 30 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, unadjusted ORs.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	OR (95% CI)
Urinary								
Gluckman	2011[99]	USA	Unclear	CAD	Mono	450 pg/mg	SVG patency	2.59 (1.20 to 5.57)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Continuous on log scale	SVG patency	1.73 (1.05 to 2.85)
Eikelboom	2002[151]	Canada	756	Miscellaneous	Mono	Q4 vs. Q1	MI	2.00 (1.19 to 3.37)
Eikelboom	2002[151]	Canada	160	Miscellaneous	Mono	Q4 vs. Q1	MI	1.30 (0.80 to 2.11)
Eikelboom	2002[151]	Canada	756	Miscellaneous	Mono	Q3 vs. Q1	MI	1.50 (0.95 to 2.37)
Eikelboom	2002[151]	Canada	160	Miscellaneous	Mono	Q3 vs. Q1	Stroke	2.50 (0.61 to 10.21)
Eikelboom	2002[151]	Canada	160	Miscellaneous	Mono	Q2 vs. Q1	Stroke	0.60 (0.20 to 1.80)
Eikelboom	2002[151]	Canada	756	Miscellaneous	Mono	Q2 vs. Q1	Stroke	0.60 (0.18 to 1.99)

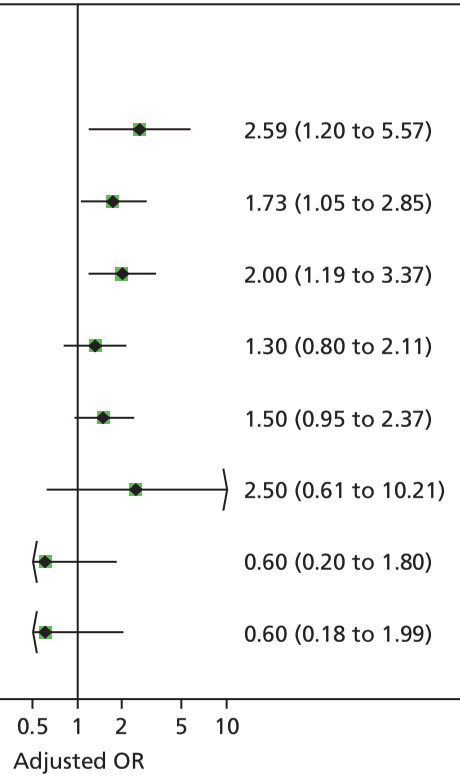

FIGURE 31 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, adjusted ORs. Q, quartile.

FIGURE 32 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, unadjusted HRs.

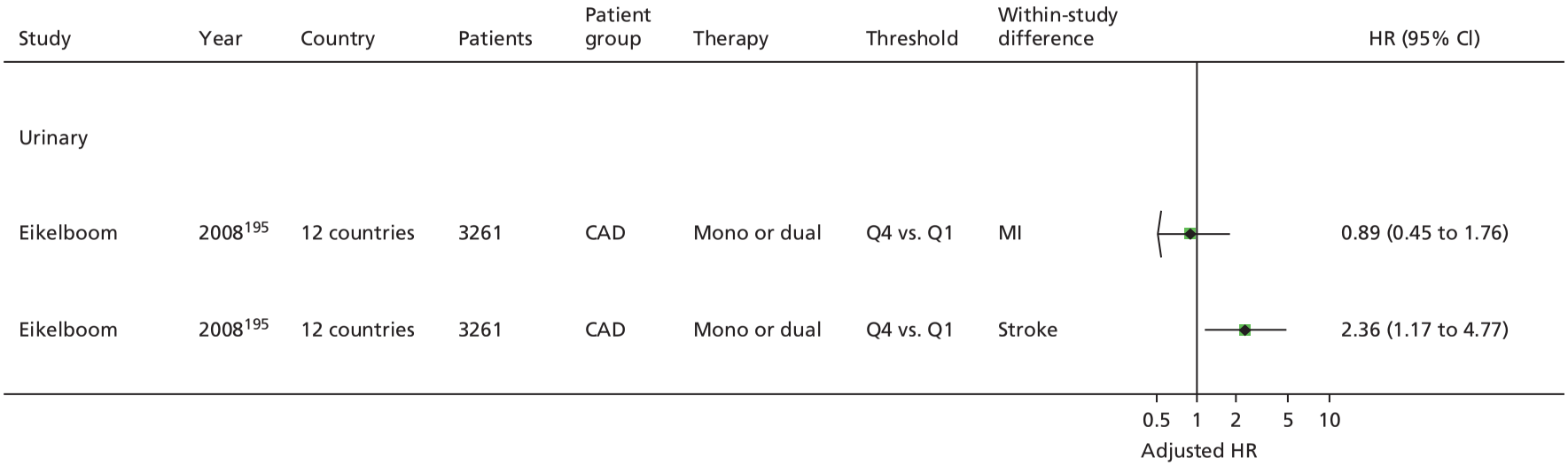

FIGURE 33 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, adjusted HRs. Q, quartile.

Bleeding events

One study reported this outcome (*Table 36*).[195]

Only one study[195] using a thromboxane test reported bleeding events [Global Utilization of Streptokinase and tPA for Occulded Coronary Arteries (GUSTO) bleeds]. The study found no significant difference when looking at a trend for bleeding rates across quartiles.

Summary: thromboxane metabolite measurement

Eleven studies were identified in this category,[46,76,99,108,110,148,151,162,164,195,202] all including stable disease populations, thus making this set of studies more homogenous in terms of population compared with studies reporting other PFTs. There was still heterogeneity, however, for example relating to specific patient characteristics and aspirin dose.

There was a lack of reporting of relevant quality criteria, making overall judgements about risk of bias difficult. No study provided details on all relevant quality criteria. Lack of details related in particular to whether or not assays were performed in a blinded manner and levels of compliance. In one study,[46] patients who stated that they were not taking their prescribed aspirin were included as a separate subgroup in the analysis (both resistant and non-compliant, as opposed to resistant and compliant). In the analysis here, these groups have been merged in order to be consistent with the other studies, where it is not possible to make this distinction. There was a lack of consistency in defining thresholds, both in methods and in actual values. Only 3[46,99,202] of 11 studies gave a predefined threshold. One study[151] used a retrospective case–control design, which is more prone to bias than prospective designs; however, as the sampling for the PFT preceded the outcomes, this study was included.

Overall, there was a consistent trend for more deaths reported in the resistant arm, with some statistically significant results, but this was based on only three studies.[76,151,195] There was also a trend for more events in the resistant groups for MACEs and ischaemic/thrombotic events, with some results showing statistical significance, but this is based on relatively few studies (no more than four studies contributed results to any one forest plot).

It is noteworthy that the direction of effect is not consistent within individual studies, reflecting different thresholds used and different outcomes (for ischaemic/thrombotic events). Some studies contributed considerably more to forest plots than others, for example where more outcomes were reported or where results could be presented for different thresholds.

Only one study[195] reported bleeding events and this found no significant difference when looking at a trend for bleeding rates across quartiles.

It was not possible to assess any differences between tests measuring thromboxane in urine or serum/plasma, as only one study[76] measuring thromboxane in serum/plasma was represented in the forest plots.

TABLE 36 Outcome measures for reporting bleeding events (thromboxane metabolite measurement, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Urinary						
Eikelboom 2008[195]					Trend across quartiles reported	

Summary: thromboxane

- Eleven studies were identified, all with stable disease populations.
- Methods for deriving thresholds and thresholds themselves were variable.
- A lack of detail on reporting of quality criteria hampered an overall risk-of-bias assessment.
- Heterogeneity in outcomes, test thresholds and types of reported statistics meant that meta-analysis was not considered appropriate.
- Adjusted results were rarely presented, and thus the additional prognostic value of the test over other prognostic factors is difficult to ascertain.
- Despite clinical heterogeneity between studies, there was a general trend for more events to occur in the 'aspirin-resistant' group for all relevant outcomes (death, MACEs, ischaemic/thrombotic events); however, this was often based on few studies and there was inconsistency in direction of effect within some studies (based on different thresholds or outcomes).
- Only one study reported bleeding events and this found no significant differences when looking at a trend for bleeding rates.
- Potential differences between measurements of thromboxane in urine or serum/plasma could not be assessed.

Platelet function analyser-100

Population and test characteristics

Twenty-one studies[76,99,108,109,112,115,116,118,123,127,132,135,137,138,144,145,150,162,186,187,189] were identified in this category, of which two[162,189] were reported in abstract form, and one[123] in the form of a letter. Populations had CAD in 10 studies,[76,99,108,112,118,127,137,144,145,162] CVD/stroke in two studies,[116,186] UA/ACS in six studies[109,115,132,135,138,187] and PAD/PVD in one study.[150] One large study ($n = 600$)[189] had a mixed population (PVD, ACS and CVD/stroke) and in one further study[123] all patients were undergoing PCI.

In one study, only patients with a first stroke were included.[186] In all other studies there were no details on how long patients had had their primary condition for.

In 19/21 studies, patients were on monotherapy at the time of the PFT and during follow-up. In the two other studies,[115,138] patients were on dual therapy during follow-up, and in one,[138] a small proportion (9%) were also on dual therapy (+ clopidogrel) at the time of the PFT.

Comedications across all studies included beta-blockers, lipid-lowering agents, anticoagulants, thrombolytic agents, ACE inhibitors, statins, heparin, COX-2 antagonists, warfarin, calcium channel blockers, diuretics, insulin, oral hypoglycaemics, antidepressants, cholesterol-lowering, antihypertensive and antidiabetic drugs, nitrate infusion and glycoprotein IIb/IIIa receptor agonists. Some studies restricted the use of some medications during a certain time period before the PFT.

Non-steroidal anti-inflammatory drugs were clearly not permitted in six studies,[108,109,112,116,186,187] and in a further study[137] they were not permitted during 7 days preceding the PFT.

The numbers of participants in the studies ranged from 51 to 700 (see *Table 37*). Where reported, mean ages ranged from 59 to 72 years, with more men than women in all studies (range 56–79%). The proportion of smokers ranged from 15% to 72% and that of diabetics from 7% to 49% (note that some proportions were presented according to resistant and sensitive groups). All studies were conducted in hospital settings.

The dose of aspirin ranged from 75 mg/day to 325 mg/day. Two studies[123,189] provided no details on dose. Details were variable across studies regarding the length of time patients had been receiving aspirin therapy prior to the PFT; where reported, the time varied from a minimum of 3 days up to 2 months. One study[144] stated that no patients were treated with antiplatelets for 10 days before undergoing CABG.

One study reported that aspirin was provided in enteric form.[99] There were no details in the other studies. The main study characteristics are reported in *Table 37*.

TABLE 37 Population characteristics (PFA-100®, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT and during follow-up										
Addad 2010,[108] Tunisia	204	Mean 59 (SD 10)	Mono	CAD	Smokers: $n = 145$ (71%) Diabetes: $n = 79$ (38.7%)	No	250 mg/day	At least 2 months	No details	No details
Aksu 2009,[109] Turkey	240 (220 eligible for analyses; population characteristics based on 220)	*Aspirin resistant:* Mean platelet volume < 8.4 fl ($n = 44$): mean 63.68 (SD 9.69) Mean platelet volume > 8.4 fl ($n = 40$): mean 62.85 (SD 12.29) *Aspirin sensitive:* Mean platelet volume < 8.4 fl ($n = 70$): mean 59.93 (SD 10.46) Mean platelet volume > 8.4 fl ($n = 66$): mean 57.42 (SD 11.97)	Mono (27% dual at follow-up)	ACS	Smokers: $n = 86$ (39%) Diabetes: $n = 107$ (49%)	No	100 mg/day (38.2%), 300 mg/day (61.8%)	At least 7 days before hospital admission	38.2	Resistant if closure time ≤ 170 seconds

continued

TABLE 37 Population characteristics (PFA-100®, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Bevilacqua 2009,[118] Italy	202	Resistant: mean 66.7 (SD 9.6) Sensitive: mean 66.2 (SD 9.9)	Mono	CAD	*Smokers:* Resistant: $n = 42$ (48.9%) Sensitive: $n = 83$ (71.6%) *Diabetes:* Resistant: $n = 34$ (39.5%) Sensitive: $n = 31$ (26.7%)	Yes: CABG	100 mg/day	At least 1 month	42.6	Resistant if closure time < 190 seconds
Boncoraglio 2009,[116] Italy	129	Mean 59 (SD 13.9)	Mono	CVD/stroke	Smokers: $n = 47$ (36.4%)	No	75–325 mg (72.1% were receiving < 160 mg/day)	At least 4 weeks	20.2	Resistant if closure time < 165 seconds
Campo 2008,[123] Italy (letter)	135 (160 in total including 25 controls; population data based on 135 patients)	Mean 65 (SD 12)	Mono (0.7% on dual at baseline, 15% on dual at follow-up)	PCI	Smokers: 33% Diabetes: 18%	No	No details	Before admission 7.4% being treated with aspirin	No details	No details
Christiaens 2008,[127] France	97	Mean 66 (SD 11)	Mono	CAD	Smokers: $n = 15$ (15%) Diabetes: $n = 15$ (15%)	No	160 mg/day	At least 1 month	29.9	Resistant if closure time < 187 seconds

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Frelinger 2009,[76] USA	700 (555 eligible for analyses)	Mean 60.7 (SEM 0.44)	Mono (32% dual during follow-up)	CAD	Smokers: 22% current (72% prior) Diabetes: 27%	No	81 or 325 mg/day	At least 3 days	8.1	Resistant if ≤ 3.1 ng/ml
Gluckman 2011,[99] USA	229	For patients with ≥ 1 occluded SVG ($n = 70$): mean 63 (range 55–72) For patients with patent SVG ($n = 159$): mean 63 (range 57–71)	Mono	CAD	Smokers: $n = 52$ (22.7%) Diabetes: $n = 84$ (36.7%)	Yes: CABG	325 mg/day	No details	No details	Resistant if closure time < 193 seconds
Hobikoglu 2007,[135] Turkey	140	Resistant: mean 63.8 (SD 10.8) Sensitive: mean 58.3 (SD 11.2)	Mono (12.1% on dual at follow-up)	ACS	*Smokers:* Resistant ($N = 45$): $n = 22$ (49%) Sensitive ($N = 79$): $n = 31$ (39%) *Diabetes:* Resistant ($N = 45$): $n = 7$ (15%) Sensitive ($N = 79$): $n = 16$ (20%)	No	100 mg/day (20% of patients); 300 mg/day (80% of patients)	At least 7 days	32.1	Resistant if closure time < 170 seconds

continued

TABLE 37 Population characteristics (PFA-100®, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Linnemann 2009,[112] Germany	98 (57 eligible for analyses)	Median 67.7 (range 44–90)	Mono	CAD	Smokers: $n = 31$ (31.6%) Diabetes: $n = 45$ (45.9%)	No	100 mg/day	At least 14 days	3.5	Resistance was the maximum aggregation values within the reference range (≥ 78%)
Lordkipanidzé 2011,[162] UK (abstract)	198	No details	Mono	CAD	No details	No	80–325 mg/day	No details	No details	No details
Modica 2009,[187] Sweden	334	Mean 72	Mono (45% dual during follow-up)	UA/ACS	Smokers: 21% Diabetes: 20%	No	75 mg/day	No details	No details	No details
Morawski 2005,[144] Poland	51	Mean 61.3 (SD 8.4)	Mono	CAD	Diabetes: 17.6%	Yes: CABG	150 mg/day	No patients were treated with antiplatelet agents for 10 days before the operation	No details	No details
Pamukcu 2007,[137] Turkey	234	Mean 57 (SD 9)	Mono (12% on dual at follow-up)	CAD	*Smokers:* Resistant ($N = 52$): $n = 32$ (61.5%) Sensitive ($N = 182$): $n = 106$ (58.2%) *Diabetes:* Resistant ($N = 52$): $n = 9$ (17.3%) Sensitive ($N = 182$): $n = 39$ (21.4%)	No	100–300 mg/day (mean dose 268 mg/day, SD 70 mg/day)	At least 7 days	22.2	Resistant if closure time < 186 seconds

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Poulsen 2007,[132] Denmark	298 (297 eligible for analyses)	*Based on 187 patients with no clinical outcomes:* Resistant ($n = 17$): mean 70 (SD 10.2) Sensitive ($n = 170$): mean 69 (SD 12)	Mono	UA/ACS	No details	No	150 mg/day	At least 7 days	70	Resistant if closure time < 165 seconds
Sambola 2004,[145] Spain	100	Mean 64 (SD 11)	Mono	CAD	No details	No	100–125 mg/day	No details	49	Resistant if closure time ≤ 193 seconds
Silver 2009,[189,193] UK (abstract)	620	Mean 72.5	Mono	Miscellaneous (PVD, ACS, CVD/stroke)	No details	No	No details	No details	25.2	Resistant if closure time < 164 seconds
Sobol 2009,[186] Poland	64 (101 enrolled: 64 stroke patients, 37 controls; all population data based on 64)	Mean 57.9 (SD 10.4)	Mono	CVD/stroke	Smokers: $n = 24$ (53.3%)	No	150 mg/day	No details	36	Resistant if closure time ≤ 150 seconds
Ziegler 2002,[150] Austria	98 (64 eligible for analyses)	Mean 66 (SD 15)	Mono (19% on dual during follow-up)	PAD/PVD	Smokers: 65.3% Diabetes: 42.9%	Yes: PTA	100 mg/day	At least 1 month	5	Resistant if closure time ≤ 170 seconds

continued

TABLE 37 Population characteristics (PFA-100®, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT, dual therapy during follow-up										
Foussas 2009,[115] Greece	496	Resistant ($n = 121$): mean 67.9 (SD 9.2) Sensitive ($n = 375$): mean 69.8 (SD 8.8)	Mono (dual during follow-up)	ACS	*Smokers:* Aspirin-resistant group ($n = 121$): 42.1% Aspirin-sensitive group ($n = 375$): 39.5% *Diabetes:* Aspirin-resistant group ($n = 121$): 24.8% Aspirin-sensitive group ($n = 375$): 34.7%	No	325 mg/day	*Prior aspirin use (≥ 7 days prior):* Aspirin-resistant group ($n = 121$): 45.5% Aspirin-sensitive group ($n = 375$): 40.3%	24.4	Resistant if closure time ≤ 193 seconds

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Fuchs 2006,[138] Austria	208	*By clinical outcomes (recurrent ACS):* Recurrent ACS ($n = 58$): mean 60 (SD 13) Event-free (number unclear): mean 57 (SD 12)	Mono, with 9% on clopidogrel at time of PFT; 92% on dual during follow-up	ACS	*By clinical outcomes (recurrent ACS):* Recurrent ACS ($n = 58$): 55% smokers Event-free (number unclear): 54% smokers Recurrent ACS ($n = 58$): 27% diabetes Event-free (number unclear): 13% diabetes	No	250 mg (assume per day)	No details	No details	Resistant if closure time < 300 seconds

PTA, percutaneous transluminal angioplasty; SEM, standard error of the mean.

All studies used the PFA-100®. The cartridge used was mainly collagen/epinephrine (CEPI), with three studies[99,150,189] additionally using collagen/ADP. One study[123] used collagen/ADP only. There were no details in one study.[162] Test characteristics are shown in *Table 38*.

Study design and quality

Results of the risk-of-bias assessment can be found in *Tables 39–42*.

Patient selection was independent of study outcome in all included studies, with the PFT preceding any outcomes (as specified in the study selection criteria). Fifteen of 21 studies stated that consecutive patients were enrolled.[76,108,112,115,116,123,127,132,135,137,138,150,186,187,189,193] Two studies[76,99] had clear details on posteligibility exclusions.

A predetermined threshold value for defining resistance was given in 18 studies;[76,99,109,112,115,116,118,123,127,132,135,137,138,145,150,186,187,189,193] thresholds varied between 150 and 193 seconds, though one study[138] had a much higher threshold at 300 seconds. One study used tertiles,[108] one used a median value and also conducted ROC analysis[123] and one[187] stated that high residual platelet reactivity was defined as a normal closure time value even when the subject was taking aspirin. There were no details on threshold in two studies.[144,162] There were a number of methods for deriving the thresholds (as reflected in the different cut-offs obtained); these included values established in previous studies or by other research groups. Only one study[108] stated that assays were performed in a blinded manner.

Outcome measures of interest were (at least partly) clearly stated in the methodology of 20 out of 21 studies. Only one study[145] did not clearly prespecify these. Ten studies[76,99,108,109,116,118,127,135,187,193] had details on blinding of outcome assessors to the PFT results. In 10 studies[108,115,118,123,127,137,144,150,186,187] it was stated or appeared that there was no loss to follow-up. There were no details in two studies.[162,193] The remaining studies reported varying proportions of loss to follow-up; this was between 8% and 58%. In the study with the largest loss to follow-up (58%),[112] data on clinical outcomes were only available for those patients who had a repeat PFT.

Compliance was measured in 11 studies[99,108,112,116,123,127,132,135,137,144,145] using interview, pill counts, self-reports and, in one study,[145] a test for salicylates in urine. Four studies[112,123,135,145] reported levels of compliance: one[123] stated that 90% of patients were still taking aspirin at year 2 (though the method of how this was ascertained was not stated); one[135] stated that all patients continued with their treatment (based on interviews); in one study,[112] patients confirmed that they had all taken aspirin over the last 14 days (based on interview); and in one study[145] patients were excluded on the basis of inadequate salicylate levels. One study[76] stated that 'Two patients had serum TXB_2 levels in the range observed for aspirin-free healthy controls, and their platelet function was therefore consistent with aspirin noncompliance; as "resistance" cannot be distinguished from noncompliance, these subjects were not excluded from follow-up.'

Nine studies[76,99,109,115,118,123,135,138,187] undertook adjusted analyses (based on HRs or ORs). There was some overlap in adjustment factors between the different studies, but no studies used all of the same ones.

TABLE 38 Test characteristics (PFA-100®, monotherapy)

Study	Details of kit	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Monotherapy at time of PFT and during follow-up				
Addad 2010[108]	PFA-100®	3.2% buffered trisodium citrate	CEPI	No details
Aksu 2009[109]	PFA-100®	3.8% citrate	CEPI	No details
Bevilacqua 2009[118]	PFA-100®	3.8% citrate	CEPI	No details
Boncoraglio 2009[116]	PFA-100®	3.8% citrate	CEPI	No details
Campo 2008[123] (letter)	PFA-100®	No details	Collagen/ADP	No details
Christiaens 2008[127]	PFA-100®	No details	CEPI	Up to 24 hours
Frelinger 2009[76]	PFA-100®	3.8% sodium citrate	CEPI	No details
Gluckman 2011[99]	PFA-100®	3.8% citrate	CEPI	No details
			Collagen/ADP	
Hobikoglu 2007[135]	PFA-100®	No details	CEPI	Up to 24 hours
Linnemann 2009[112]	PFA-100®	0.129 M (3.8%) trisodium citrate	CEPI	1–24 hours
Lordkipanidzé 2011[162] (abstract)	PFA-100®	No details	No details	No details
Modica 2009[187]	PFA-100®	No details	Epinephrine (30 µl of a solution containing 0.1 mg epinephrine)	Up to 24 hours
Morawski 2005[144]	PFA-100®	No details	CEPI	Up to 12 hours
Pamukcu 2007[137]	PFA-100®	No details	CEPI	1–4 hours
Poulsen 2007[132]	PFA-100®	No details	CEPI	Up to 24 hours
Sambola 2004[145]	PFA-100®	0.128 M buffered sodium citrate	CEPI	Approximately 3 hours
Silver 2009[189,193] (abstract)	PFA-100®	No details	CEPI	No details
			Collagen/ADP	
Sobol 2009[186]	PFA-100®	No details	CEPI	First test: before aspirin
				Second test: up to 24 hours
Ziegler 2002[150]	PFA-100®	No details	CEPI	Up to 24 hours
			Collagen/ADP	
Monotherapy at time of PFT, dual therapy during follow-up				
Foussas 2009[115]	PFA-100®	No details	CEPI	Up to 24 hours
Fuchs 2006[138]	PFA-100®	129 mM buffered sodium citrate	CEPI	No details

TABLE 39 Risk of bias, patient selection (PFA-100®, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Monotherapy at time of PFT and during follow-up			
Addad 2010[108]	Consecutive	Yes	No details
Aksu 2009[109]	No details	Yes	No details
Bevilacqua 2009[118]	All patients undergoing isolated primary CABG surgery over the course of 1 year	Yes	Appears that no eligible patients were excluded
Boncoraglio 2009[116]	Consecutive	Yes	No details
Campo 2008[123]	Consecutive	Yes	No details
Christiaens 2008[127]	Consecutive	Yes	No details
Frelinger 2009[76]	Consecutive	Yes	Stated that less than 3% of eligible patients declined participation (reason not given)
Gluckman 2011[99]	No details	Yes	Patients in whom SVG patency not assessed or those not on aspirin monotherapy. Authors stated that the study population was representative of patients undergoing isolated CABG surgery based on comparison with the Society of Thoracic Surgeons National Database
Hobikoglu 2007[135]	Consecutive	Yes	No details
Linnemann 2009[112]	Consecutive	Yes	No details
Lordkipanidzé 2011[162] (abstract)	No details	Yes	No details
Modica 2009[187]	Consecutive	Yes	No details
Morawski 2005[144]	No details for whole sample, patients randomly assigned to aspirin or placebo	Yes	No details
Pamukcu 2007[137]	Consecutive	Yes	No details
Poulsen 2007[132]	Consecutive	Yes	No details
Sambola 2004[145]	No details	Yes	No details
Silver 2009[189,193] (abstract)	Consecutive	Yes	No details
Sobol 2009[186]	Consecutive	Yes	No details
Ziegler 2002[150]	Consecutive	Yes	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Foussas 2009[115]	Consecutive	Yes	No details
Fuchs 2006[138]	Consecutive	Yes	No details

TABLE 40 Risk of bias, PFT (PFA-100®, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Monotherapy at time of PFT and during follow-up			
Addad 2010[108]	No (tertiles)	Tertiles	Yes; stated that all assays were performed in a blinded manner
Aksu 2009[109]	Yes; stated (wrongly) that resistant if CEPI CT of ≥ 170 seconds, but appears that subsequent figures relate to correct definition (i.e. resistant if ≤ 170 seconds)	As described in authors' previous studies	No details
Bevilacqua 2009[118]	Yes (< 190 seconds)	Reference cited[222]	No details
Boncoraglio 2009[116]	Yes (< 165 seconds)	Manufacturer's information, corroborated in authors' laboratory	No details
Campo 2008[123]	Yes (for CADP)	For CADP: median value as cut-off between high and low platelet reactivity; also ROC analysis for exploratory evaluation of best cut-off For CEPI: no details	No details
Christiaens 2008[127]	Yes (< 187 seconds)	Previously established in authors' laboratory	No details
Frelinger 2009[76]	Yes (≤ 193 seconds)	Cut-off represents the upper limit of the 90% central interval of duplicate results measured in an aspirin-free healthy population (references given)	No details
Gluckman 2011[99]	Yes (≤ 193 seconds)	The upper limit of the normal range in the authors' laboratory for aspirin-naive patients	No details
Hobikoglu 2007[135]	Yes (< 170 seconds)	Mean (+ 2 SD) CT of healthy volunteers not on aspirin. Aspirin resistance defined as a normal CT (below the control group cut-off value) despite aspirin treatment	No details
Linnemann 2009[112]	Yes (CT < 192 seconds)	Previously determined by the research group from the 95th percentile of measurements in a group of 50 healthy volunteers	No details
Lordkipanidzé 2011[162] (abstract)	No details	No details	No details

continued

TABLE 40 Risk of bias, PFT (PFA-100®, monotherapy) (*continued*)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Modica 2009[187]	Yes	No specific value; high residual platelet reactivity defined as a normal CT value even when the subject was taking aspirin (reference cited[77]). In-house reference ranges were established from analyses in a control group of 278 volunteers	No details
Morawski 2005[144]	No details	No details (appears authors were trying to measure a correlation between the CT and postoperative bleeding)	No details
Pamukcu 2007[137]	Yes (CT < 186 seconds)	Reference cited[223] for normal reference range (98–185 seconds) for the PFA-100® with CEPI cartridges	No details
Poulsen 2007[132]	Yes (CT < 165 seconds for CEPI; no details for CADP)	Cut-off value based on the results from a previous study evaluating the performance of the PFA-100® in patients taking aspirin	No details
Sambola 2004[145]	Yes (CT ≤ 137 seconds)	Reference cited[224]	No details
Silver 2009[189,193] (abstract)	Yes (CT < 164 seconds for CEPI; no details for CADP)	No details	No details
Sobol 2009[186]	Yes (CT ≤ 150 seconds)	No details	No details
Ziegler 2002[150]	Yes (CT < 170 seconds during at least one follow-up visit)	No details	No details
Monotherapy at time of PFT, dual therapy during follow-up			
Foussas 2009[115]	Yes (CT ≤ 193 seconds)	References cited[219,225]	No details
Fuchs 2006[138]	Yes (CT < 300 seconds)	For this purpose CEPI CT was stratified according to values > or < 300 seconds, as 77% of the ACS patients reached the maximal CT value of 300 seconds after aspirin infusion. Quartiles also used in analysis	No details

CADP, collagen/ADP; CT, closure time.

TABLE 41 Risk of bias, outcomes and study attrition (PFA-100®, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Monotherapy at time of PFT and during follow-up			
Addad 2010[108]	Yes	Yes; follow-up clinicians were blinded to PFT results	Stated that none of the included patients was lost to follow-up
Aksu 2009[109]	Yes	Yes; people performing follow-up interviews were blind to aspirin resistance and mean platelet volume status of the patients	20/240 lost to follow-up; reasons not stated. Analyses based on 220
Bevilacqua 2009[118]	Yes	Yes; follow-up visits conducted by cardiologists not involved in the present study	Stated that follow-up 100% complete
Boncoraglio 2009[116]	Partly (vascular cognitive impairment is mentioned in results, but not as part of composite outcome defined in methods)	Yes; personnel responsible for data collection were not aware of PFT results	13/142 lost to follow-up (seven had changed address and telephone number, four refused to reply to the questions and two had stopped taking aspirin for reasons unconnected with vascular disease)
Campo 2008[123]	Yes	No details	Appears there was loss to follow-up
Christiaens 2008[127]	Yes	Yes; observers collecting follow-up data were blinded to the PFT results	All patients who enrolled completed the study
Frelinger 2009[76]	Yes	Yes; all clinical outcome data obtained by research personnel blinded to results of PFTs	127/682 not included in follow-up (appears test not done in everyone)
Gluckman 2011[99]	Yes	Yes; stated that images were analysed by two blinded reviewers (98% concordance) with a third reviewer adjudicating as necessary	73/229 not included at follow-up
Hobikoglu 2007[135]	Yes	Yes; scores were determined by one of the investigators, who had no knowledge of the presence of aspirin resistance	16/140 lost to follow-up and excluded from analysis
Linnemann 2009[112]	Yes	Unclear; reported events were only considered if they were confirmed by medical reports from GPs or admitting hospitals	Data on clinical outcome available only from patients whose platelet function was assessed twice (57/98). Of the 41 excluded, 4 patients died and 16 had their antithrombotic medication changed. Remaining reasons for dropouts not stated. Authors state that there was no difference observed in aspirin resistance rates between dropouts and those remaining in study
Lordkipanidzé 2011[162] (abstract)	Yes	No details	No details

continued

TABLE 41 Risk of bias, outcomes and study attrition (PFA-100®, monotherapy) (*continued*)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Modica 2009[187]	Yes	Yes; states that the test results were not accessible by the attending physicians	Stated that no patients were lost to follow-up
Morawski 2005[144]	Yes	No details	Appears to be no loss to follow-up
Pamukcu 2007[137]	Yes	No details	Appears to be no loss to follow-up
Poulsen 2007[132]	Yes	No details	Stated that patients were excluded from follow-up if they were no longer taking aspirin, had suffered an acute MI or stroke, or had undergone mechanical revascularisation because of atherothrombotic disease within the previous 3 months 111/298 excluded from the follow-up visit for the following reasons: death ($n = 39$), withdrawal of aspirin treatment ($n = 27$), unwillingness to participate ($n = 35$), geographical reasons ($n = 5$), recurrent MI or stroke within the last 3 months ($n = 4$). One participant was lost to follow-up Even though these patients were excluded, clinical outcomes are linked to the full sample (297/298 patients)
Sambola 2004[145]	No	No details	19/100 patients lost to follow-up at 6 months. Five cardiovascular deaths and 14 patients excluded [9 declared non-compliant with aspirin treatment based on interview, 5 treated with other regimens (3 clopidogrel, 2 warfarin)]
Silver 2009[189,193] (abstract)	Yes	Yes; treating physicians, patients and researchers were blind to the test results	No details
Sobol 2009[186]	Yes	No details	No losses to follow-up
Ziegler 2002[150]	Yes	No details	Appears that there was no loss to follow-up
Monotherapy at time of PFT, dual therapy during follow-up			
Foussas 2009[115]	Yes (for one outcome) No (for two outcomes)	No details	Stated that no patients lost during follow-up
Fuchs 2006[138]	Yes	No details	13% of patients lost to follow-up (6% in the first year)

TABLE 42 Risk of bias, confounders (PFA-100®, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Monotherapy at time of PFT and during follow-up						
Addad 2010[108]	Design: N/A Analysis: no (for groups by aspirin responder status)	N/A	No details	Yes	Interview at study enrolment and during follow-up period	No details
Aksu 2009[109]	Design: N/A Analysis: yes (HR)	Troponin T, platelet number, severity score and neutrophil percentage in WBC count (but groups not defined on basis of aspirin resistance alone)	No details	No details	No details	No details
Bevilacqua 2009[118]	Design: N/A Analysis: yes (HR)	Age, male sex, diabetes, hypertension, obesity, hypercholesterolaemia, smoking habit, left ventricular ejection fraction, logistic EuroSCORE, incomplete revascularisation	No details	No details	No details	No details
Boncoraglio 2009[116]	Design: N/A Analysis: no	N/A	No details	Yes	Telephone interview using standardised questionnaire (as part of outcome assessment)	No details
Campo 2008[123]	Design: N/A Analysis: yes (HR)	Not specified	No details	Yes	No details	At 1 year, 116 (91%) patients still taking aspirin; at 2 years, 112 (90%) still taking aspirin

continued

TABLE 42 Risk of bias, confounders (PFA-100®, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Christiaens 2008[127]	Design: N/A Analysis: no	N/A	No details	Yes	Personal interview at the time of inclusion	No details
Frelinger 2009[76]	Design: N/A Analysis: yes (OR)	Sex, TIMI risk score, aspirin dose, platelet count, BMI, use of clopidogrel, statins and oral hypoglycaemic agents	N/A	Not mentioned in methods, but a TxB_2 test undertaken and stated that: 'Two patients had serum TXB_2 levels in the range observed for aspirin-free healthy controls, and their platelet function was therefore consistent with aspirin noncompliance. Because "resistance" cannot be distinguished from noncompliance, these subjects were not excluded from follow-up'		
Gluckman 2011[99]	Design: N/A Analysis: yes (OR)	Target vessel diameter, thromboxane levels, sex, (race in one model)	N/A	Yes	Pill counts at each postoperative encounter	No details
Hobikoglu 2007[135]	Design: N/A Analysis: yes (HR)	Age, platelet count, cTnT value and CAD severity score	No details	Yes	Self-report; telephone interviews at follow-up	According to the follow-up visits, all patients continued on 100 mg aspirin, and none of them discontinued treatment
Linnemann 2009[112]	Design: N/A Analysis: no	N/A	N/A	Yes	Interview at study commencement and follow-up	'All patients confirmed that they had taken aspirin regularly as directed over the last 14 days.' Not clear which time period this relates to; probably the start of the study
Lordkipanidzé 2011[162] (abstract)	Design: N/A Analysis: unclear whether adjusted or unadjusted OR	No details	N/A	No details	No details	No details

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Modica 2009[187]	Design: N/A Analysis: yes (HR)	Age, sex, diabetes, smoking status, heart failure, atrial fibrillation, baseline glomerular filtration rate, troponin T, platelet aggregation, high residual platelet reactivity, intervention with CABG or PCI	Yes (the assumptions for Cox regression analysis were evaluated by Kaplan–Meier curves for all the variables included)	No details	No details	No details
Morawski 2005[144]	Design: N/A Analysis: no	N/A	N/A	Yes	Aspirin was administered under controlled conditions	No details; likely to be 100% owing to RCT conditions
Pamukcu 2007[137]	Design: N/A Analysis: no	N/A	No details	Yes	States that: 'Compliance with aspirin therapy was ascertained by a personal interview'	No details
Poulsen 2007[132]	Design: N/A Analysis: no	N/A	No details	Yes	The patients were informed that they should take their usual aspirin 3–5 hours before blood sampling on the day of the follow-up visit. During the last week before the follow-up visit, the same investigator telephoned all patients on a daily basis to ensure that each patient remembered to take her/his daily dose of aspirin	No details

continued

TABLE 42 Risk of bias, confounders (PFA-100®, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Sambola 2004[145]	Design: N/A Analysis: no	N/A	N/A	Yes	Personal interview at 1 and 6 months; biochemical test for salicylates in urine (not clear at which time point)	The levels of salicylate in urine for patients with good response to aspirin and resistance were 88 ± 88 mg/ml vs.78 ± 45 mg/ml, p = NS, at 1 month, and 89 ± 91 mg/ml vs. 77 ± 67 mg/ml, p = NS, at 6 months Six patients with good response to aspirin and four patients with resistance showed inadequate salicylate levels in urine (< 30 mg/ml), at both 1 and 6 months. After excluding these 10 patients, the salicylate levels were not significantly different between groups (95 ± 91mg/ml vs. 84 ± 41 mg/ml, p = NS, at 1 month; 99 ± 93 mg/ml vs. 86 ± 68 mg/ml, p = NS, at 6 months) All patients with recurrence of ischaemic events had adequate salicylate levels

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Silver 2009[189,193] (abstract)	Design: N/A Analysis: no	N/A	No details	No details	No details	No details
Sobol 2009[186]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Ziegler 2002[150]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Monotherapy at time of PFT, dual therapy during follow-up						
Foussas 2009[115]	Design: N/A Analysis: yes (HR)	Age, sex, smoking, diabetes, history of MI, history of coronary bypass grafting, prior aspirin use (≥ 7 days prior), cTnI ≥ 0.4 ng/ml, hs-CRP ≥ 3 mg/l, TIMI risk score, left ventricular ejection fraction < 35%	No details	No details	No details	No details
Fuchs 2006[138]	Design: N/A Analysis: yes (HR)	Diabetes, beta-blockers, clopidogrel, von Willebrand factor: ristocetin cofactor	No details	No details	No details	No details

BMI, body mass index; cTnI, cardiac troponin I; cTnT, cardiac troponin T; EuroSCORE, European System for Cardiac Operative Risk Evaluation; hs-CRP, high-sensitivity C-reactive protein; N/A, not applicable; NS, not significant; RCT, randomised controlled trial; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell.

Overview of outcomes

Twenty-one studies were found in this category,[76,99,108,109,112,115,116,118,123,127,132,135,137,138,144,145,150,162,186,187,189] with MACEs being the most frequently reported outcome (*Table 43*). Bleeding events were reported in one study only.[144]

Death

Death rates were reported in 10 studies (*Table 44*).[76,109,115,118,127,132,135,137,145,186] Outcome statistics are shown in *Figures 34–36*. Results for three of these could not be presented in forest plots. In the study by Aksu *et al.*,[109] results were presented according to both resistance status and a cut-off for mean platelet volume. One group (resistant and mean platelet volume > 8.4 fl) has an increased event rate compared with the other three groups, but it is unclear how much the resistance is contributing to this. In the study by Sobol *et al.*,[186] one death occurred in the resistant group, but it was unclear if this was in the group classified as resistant with PFA-100® or WBA. Frelinger *et al.*[76] does not present deaths separately by resistant and sensitive groups.

TABLE 43 Outcomes (PFA-100®, monotherapy)

Study	Death	MACE	Ischaemic/thrombotic	Bleeding	Length of follow-up
Monotherapy at time of PFT and during follow-up					
Addad 2010[108]		✓			1 year
Aksu 2009[109]	✓	✓	✓		Mean 14.86 (SD 5.93) months
Bevilacqua 2009[118]	✓	✓	✓		Mean 32 (SD 10) months
Boncoraglio 2009[116]		✓			Mean 56.6 (range 32–91) months
Campo 2008[123]		✓			2 years
Christiaens 2008[127]	✓	✓	✓		Median 2.5 years
Frelinger 2009[76]	✓	✓			Mean 24.8 (SD 0.3) months
Gluckman 2011[99]			✓		6 months
Hobikoglu 2007[135]	✓	✓	✓		Mean 20 (range 18–24) months
Linnemann 2009[112]		✓	✓		Median 17 (range 10–37) months
Lordkipanidzé 2011[162] (abstract)		✓			3 years
Modica 2009[187]		✓			Median 44 (IQR 35–55) months
Morawski 2005[144]				✓	7 days
Pamukcu 2007[137]	✓	✓			Mean 20.6 (SD 6.9) months
Poulsen 2007[132]	✓	✓	✓		1 year
Sambola 2004[145]	✓		✓		6 months
Silver 2009[189,193] (abstract)			✓		Unclear; 2268 patient-years of follow-up between 2002 and 2004
Sobol 2009[186]	✓				10 days
Ziegler 2002[150]			✓		1 year
Monotherapy at time of PFT, dual therapy during follow-up					
Foussas 2009[115]	✓		✓		1 year
Fuchs 2006[138]		✓			Mean 859 (range 830–887) days

IQR, interquartile range.

TABLE 44 Outcome measures for reporting death (PFA-100®, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Aksu 2009[109]					Results not presented according to resistant and sensitive only, but also depending on mean platelet volume	
Bevilacqua 2009[118]	✓[a]		✓[a]			✓[a]
Christiaens 2008[127]	✓[a]		✓[a]			✓[a]
Frelinger 2009[76]					Total number of deaths reported by resistant or sensitive groups unclear	
Hobikoglu 2007[135]			✓			
Pamukcu 2007[137]	✓[a]		✓[a]			✓[a]
Poulsen 2007[132]	✓[a]		✓[a]			✓[a]
Sambola 2004[145]	✓[a]		✓[a]			✓[a]
Sobol 2009[186]					Unclear if event in resistant group defined by PFA-100® or WBA	
Monotherapy at time of PFT, dual therapy during follow-up						
Foussas 2009[115]			✓			

a Calculated from data given in the publication.

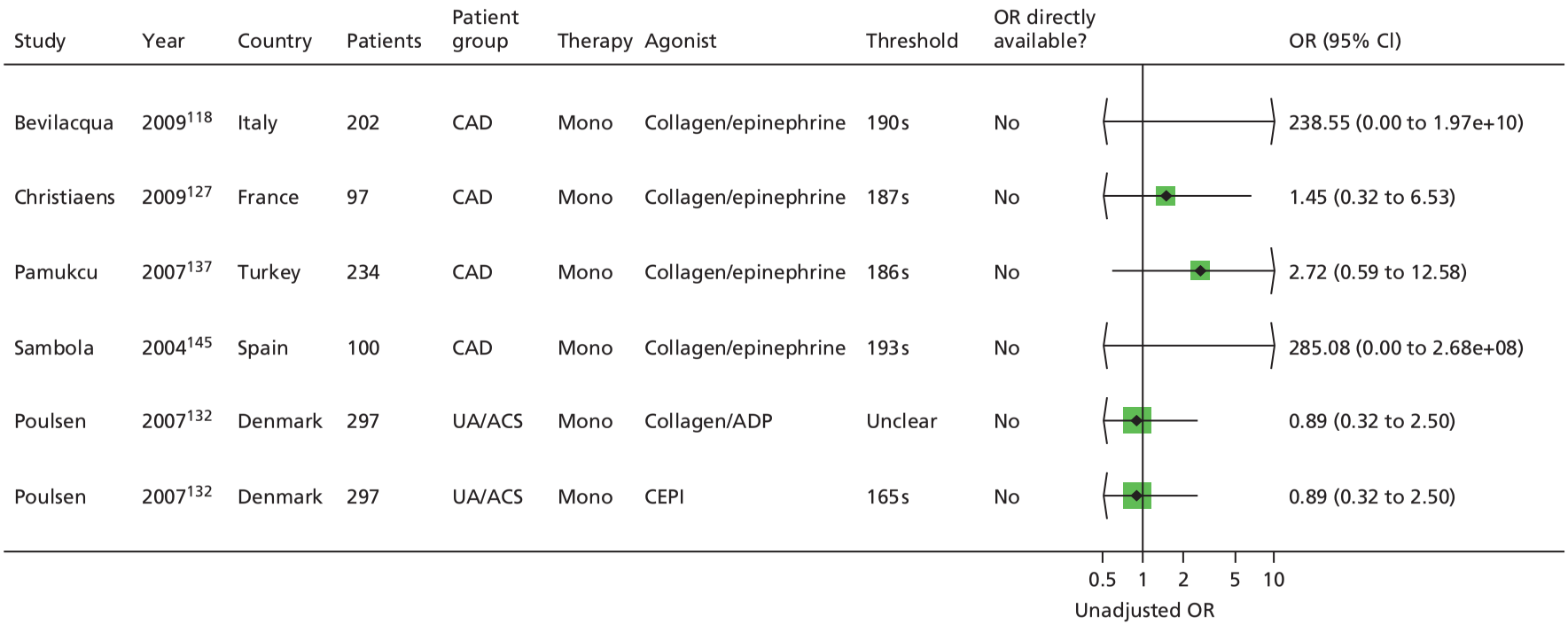

FIGURE 34 PFA-100®, monotherapy: death, unadjusted ORs. s, seconds.

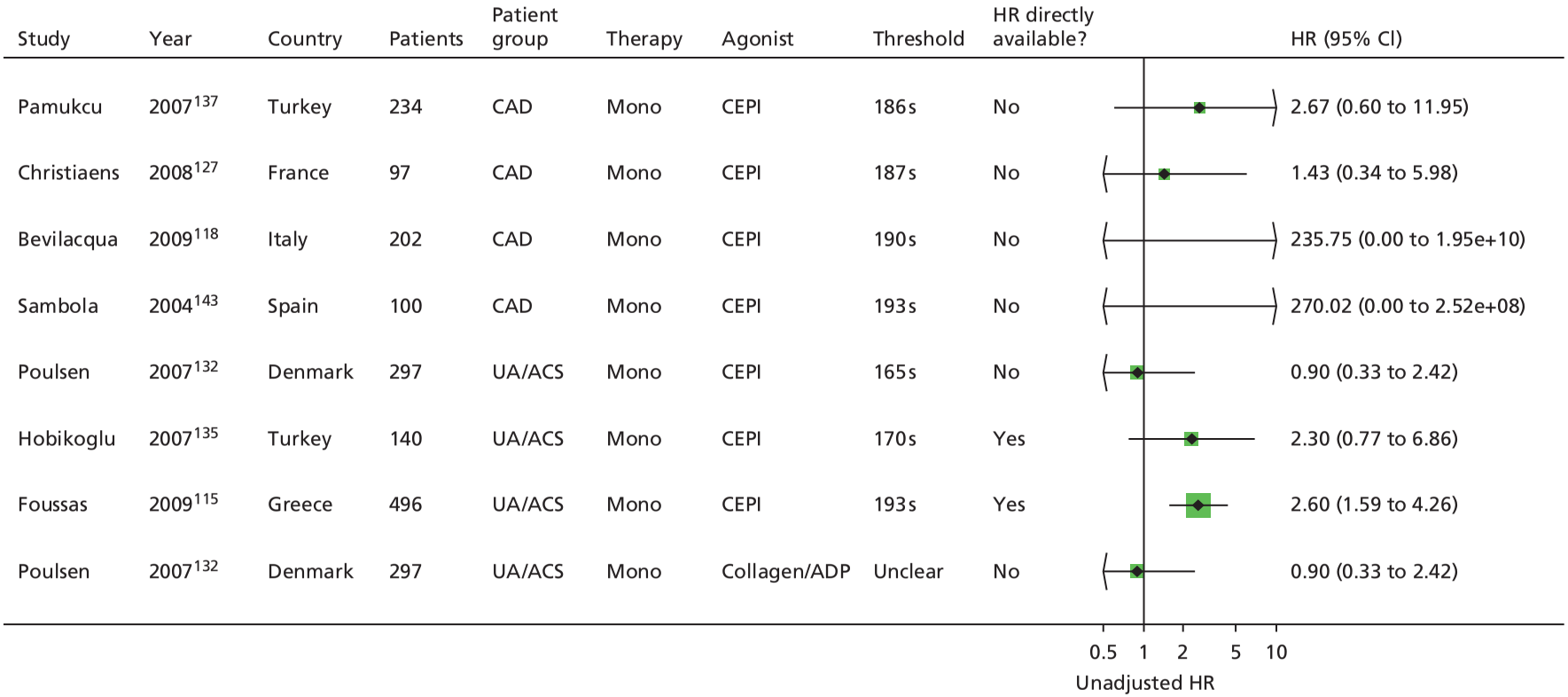

FIGURE 35 PFA-100®, monotherapy: death, unadjusted HRs. s, seconds.

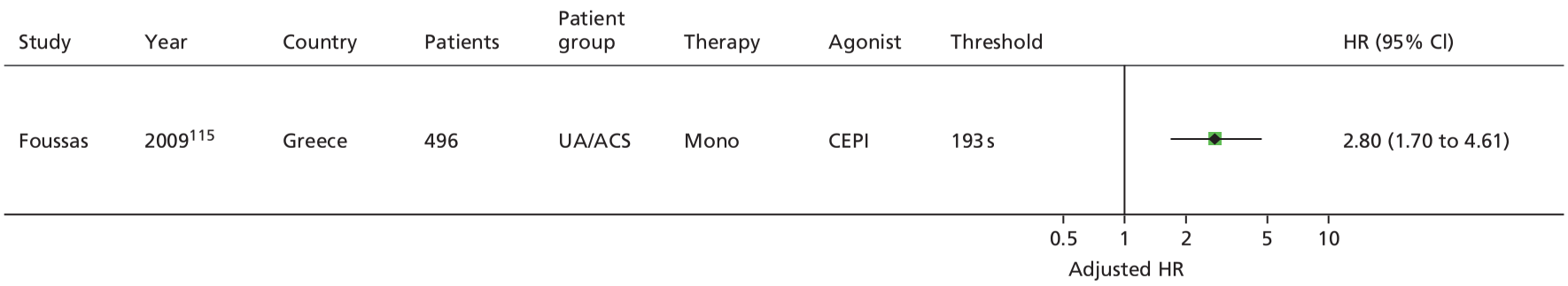

FIGURE 36 PFA-100®, monotherapy: death, adjusted HRs. s, seconds.

Six unadjusted ORs are presented based on five studies.[118,127,132,137,145] There were more events in the resistant arm in four of the five studies,[118,127,137,145] but no differences were statistically significant. Seven of eight unadjusted HRs (based on seven studies[115,118,127,132,135,137,145]) are also not statistically significant. Note that the very large ORs and HRs[118,145] are based on two[118] and five[145] events respectively in the resistant group and zero events in the sensitive group. The one statistically significant result (unadjusted HR) remained statistically significant after adjustment; this was in a UA/ACS population.[115]

Overall, there was a trend towards more deaths in the resistant groups, but most results were not statistically significant.

TABLE 45 Outcome measures for reporting MACEs (PFA-100®, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Addad 2010[108]	✓[a]		✓[a]	✓		✓[a]
Aksu 2009[109]	✓[a]		✓[a]			✓[a]
Bevilacqua 2009[118]			✓			
Boncoraglio 2009[116]	✓[a]		✓[a]			✓[a]
Campo 2008[123]				✓		
Christiaens 2008[127]	✓[a]		✓[a]			✓[a]
Frelinger 2009[76]					OR reported in graph only, but not exact numbers	
Hobikoglu 2007[135]	✓[a]		✓	✓		✓[a]
Linnemann 2009[112]	✓[a]		✓[a]			✓[a]
Lordkipanidzé 2011[162] (abstract)	✓					
Modica 2009[187]			✓	✓		
Pamukcu 2007[137]	✓[a]		✓[a]			✓[a]
Poulsen 2007[132]	✓[a]		✓[a]			✓[a]
Monotherapy at time of PFT, dual therapy during follow-up						
Fuchs 2006[138]			✓	✓		

a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	143s	First tertile vs. second and third tertile (RAVE)	No	6.33 (1.24 to 32.26)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	143s	First tertile vs. second and third tertile (MACE)	No	1.69 (0.66 to 4.30)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	298s	First and second tertile vs. third tertile (RAVE)	No	579.06 (0.00 to 4.95e+12)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	298s	First and second tertile vs. third tertile (MACE)	No	1.56 (0.54 to 4.49)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187s		No	1.37 (0.41 to 4.50)
Lordkipanidzé	2011[162]	Canada	198	CAD	Mono	Not stated	No details		Yes	1.30 (0.51 to 3.29)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186s		No	1.47 (0.61 to 3.57)
Boncoraglio	2009[116]	Italy	129	CVD/ stroke	Mono	CEPI	165s		No	1.07 (0.32 to 3.53)
Linnemann	2009[112]	Germany	57	PAD/ PVD	Mono	CEPI	192s		No	0.01 (0.00 to 2679.07)
Aksu	2009[109]	Turkey	220	UA/ACS	Mono at baseline; follow-up 73% mono, 27% dual	CEPI	170s		No	3.17 (1.71 to 5.90)
Hobikoglu	2007[133]	Turkey	140	UA/ACS	Mono	CEPI	170s		No	2.80 (1.19 to 6.57)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165s	Death, MI, or stroke	No	1.06 (0.52 to 2.17)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ ADP	Unclear	Death, MI, or stroke and revascularisation	No	0.93 (0.50 to 1.74)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ ADP	Unclear	Death, MI, or stroke	No	1.06 (0.52 to 2.17)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Death, MI, or stroke and revascularisation	No	0.93 (0.50 to 1.74)

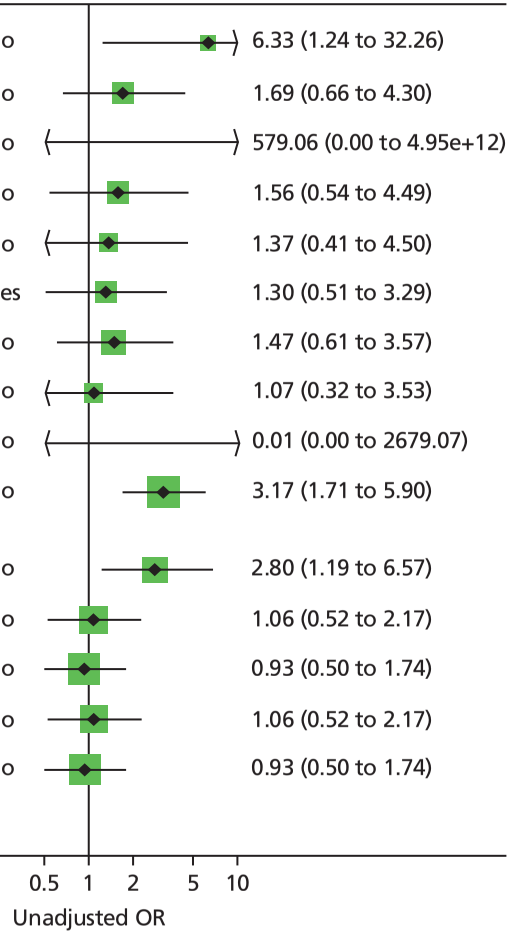

FIGURE 37 PFA-100®, monotherapy: MACEs, unadjusted ORs. RAVE, recurrent acute vascular event; s, seconds.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (MACE)	No	1.64 (0.68 to 3.97)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	298 s	First and second tertile vs. third tertile (RAVE)	No	561.68 (0.00 to 4.79e+12)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (RAVE)	No	6.09 (1.23 to 30.20)
Addad	2010[108]	Tunisia/ France	204	CAD	Mono	CEPI	298 s	First and second tertile vs. third tertile (MACE)	No	1.53 (0.56 to 4.21)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s		Yes	2.11 (1.33 to 3.34)
Christaens	2008[127]	France	97	CAD	Mono	CEPI	187 s		No	1.33 (0.45 to 3.98)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186 s		No	1.44 (0.63 to 3.26)
Boncoraglio	2009[116]	Italy	129	CVD/ stroke	Mono	CEPI	165 s		No	1.07 (0.35 to 3.30)
Linnemann	2009[112]	Germany	57	PAD/ PVD	Mono	CEPI	192 s		No	0.01 (0.00 to 2792.29)
Aksu	2009[109]	Turkey	220	UA/ACS	Mono at baseline; follow-up 73% mono, 27% dual	CEPI	170 s		No	2.67 (1.58 to 4.51)
Fuchs	2006[138]	Austria	208	UA/ACS	Mono	CEPI	300 s	Recurrence of ACS	Yes	2.00 (1.11 to 3.62)
Fuchs	2006[138]	Austria	208	UA/ACS	Mono	Collagen/ADP	High vs. low quartile	Recurrence of ACS	Yes	3.30 (1.44 to 7.59)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s		Yes	2.32 (1.11 to 4.84)
Modica	2009[187]	Sweden	334	UA/ACS	Mono	Epinephrine	Quartiles		Yes	0.80 (0.54 to 1.19)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Not clear	Death, MI, stroke or revascularisation	No	0.94 (0.55 to 1.62)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, or stroke	No	1.06 (0.55 to 2.03)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Not clear	Death, MI, or stroke	No	1.06 (0.55 to 2.03)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, stroke or revascularisation	No	0.94 (0.55 to 1.62)

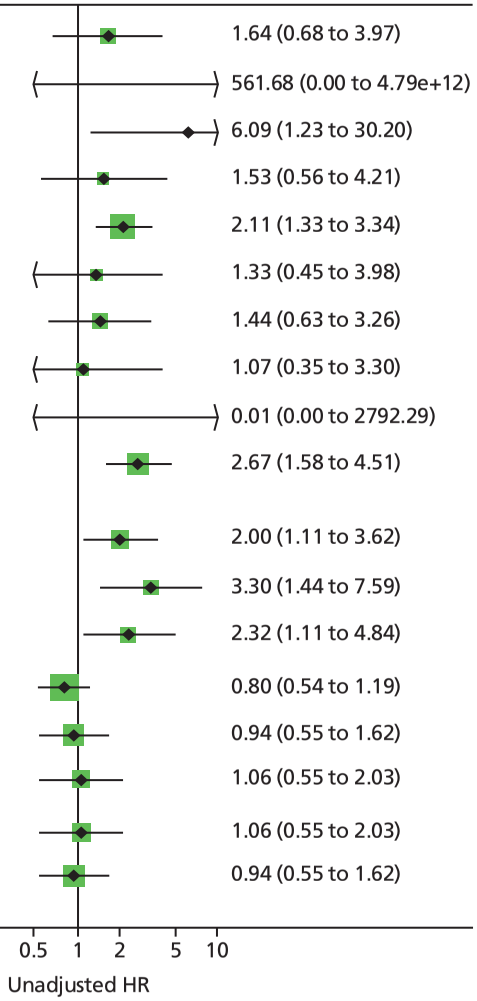

FIGURE 38 PFA-100®, monotherapy: MACEs, unadjusted HRs. RAVE, recurrent acute vascular event; s, seconds.

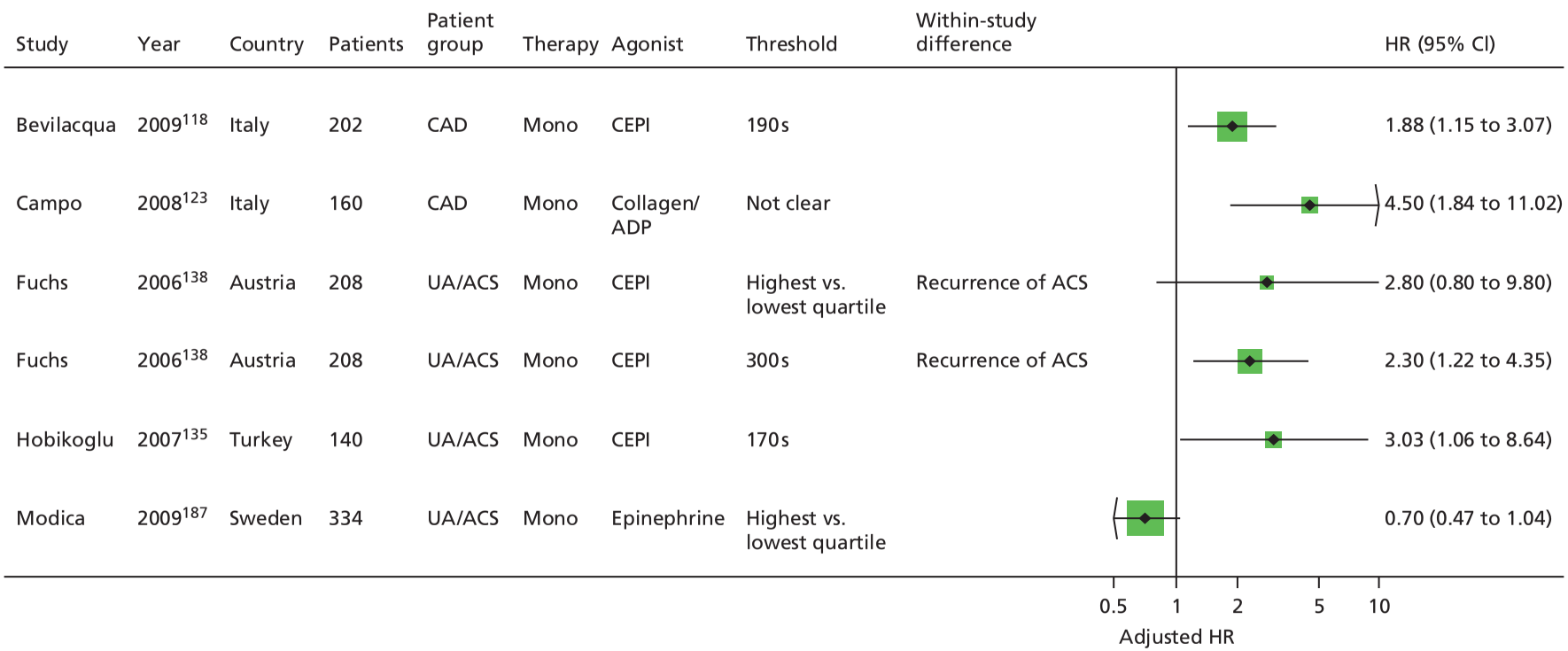

FIGURE 39 PFA-100®, monotherapy: MACEs, adjusted HRs. s, seconds.

Major adverse cardiac events

Fourteen studies reported MACEs (*Table 45*).[76,108,109,112,116,118,123,127,132,135,137,138,162,187] Outcome statistics are shown in *Figures 37–39*. One[76] was not presented in a forest plot as exact numbers were not reported. The graphical representation indicates an unadjusted OR below 1 (more events in the sensitive group), but this was not statistically significant.

Fifteen unadjusted ORs are presented, based on nine studies;[108,109,112,116,127,132,135,137,162] note that two[108,132] of these studies contribute four results each. Three ORs are statistically significant (more events in the resistant group), based on three studies.[108,109,135] Apart from one study[132] contributing four results which are all close to 1, the direction of effect based on the other eight studies[108,109,112,116,127,135,137,162] is consistent (more events in the resistant groups). Note that six results are based on three studies[109,132,135] with an acute population.

Eighteen unadjusted HRs are presented, based on 11 studies.[108,109,112,116,118,127,132,135,137,138,187] Two[108,132] of these studies contribute four results each. With the exception of two studies,[132,187] the direction of effect is again consistent (more events in the resistant arm). Six unadjusted HRs (based on five studies[108,109,118,135,138]) were statistically significant.

Six adjusted HRs (based on five studies[118,123,135,138,187]) were available, four of which were statistically significant (more events in the resistant arm). One study[187] clearly shows the opposite direction of effect (though this is not statistically significant); this may be a result of differences in threshold (highest vs. lowest quartile was compared rather than using a single cut-off), population differences or differences in adjustment factors.

Overall, there was a mainly consistent trend, with more MACEs in the resistant arm, and some results were statistically significant. Not all studies contributed to the results, particularly the adjusted results. In addition, five of six unadjusted HRs were based on an acute population, which may not be representative of the general population prescribed aspirin monotherapy.

Ischaemic/thrombotic events

Eleven studies reported additional ischaemic/thrombotic outcomes (*Table 46*).[99,109,112,115,118,127,132,135,145,150,189,193] Results from two studies could not be presented in the forest plots. In the study by Aksu *et al.*,[109] results were presented according to both resistance status and a cut-off for mean platelet volume. One group (resistant and mean platelet volume > 8.4 fl) had an increased event rate compared with the other three groups, but it was unclear how much the resistance was contributing to this. Sambola *et al.*[145] stated that no significant differences were found between resistant and sensitive groups in rates of infarction, angina or need for revascularisation.

Outcome statistics are shown in *Figures 40–43*. Nineteen unadjusted ORs were presented based on seven studies.[99,112,115,118,127,132,150] Two ORs were statistically significant (more events in the resistant group), but for one of these (from the Gluckman *et al.* study[99]) the threshold was unclear. Note that eight ORs are derived from populations with UA/ACS. The overall direction of effect was not consistent across (or within, e.g. Poulsen *et al.*,[132] Linnemann *et al.*[112]) studies. There were two adjusted ORs (based on one study[99]), one of which was statistically significant (more events in the resistant group).

Two of 22 unadjusted HRs were statistically significant (more events in the resistant group); however, the direction of effect was again not consistent. Eleven of the 21 ORs were based on populations with UA/ACS. Note also that some studies contributed disproportionately to the results, for example where they measured more outcomes. There was only one adjusted HR, showing a statistically significant result (more events in the resistant group).

TABLE 46 Outcome measures for reporting ischaemic/thrombotic events (PFA-100®, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Aksu 2009[109]					Results not presented according to resistant and sensitive only, but also depending on mean platelet volume	
Bevilacqua 2009[118]	✓[a]		✓	✓		✓[a]
Christiaens 2008[127]	✓[a]		✓[a]			✓[a]
Gluckman 2011[99]	✓	✓				
Hobikoglu 2007[135]			✓			
Linnemann 2009[112]	✓[a]		✓[a]			✓[a]
Poulsen 2007[132]	✓[a]		✓[a]			✓[a]
Sambola 2004[145]					Narrative description	
Silver 2009[189,193] (abstract)			✓			
Ziegler 2002[150]	✓[a]		✓[a]			✓[a]
Monotherapy at time of PFT, dual therapy during follow-up						
Foussas 2009[115]	✓[a]		✓[a]			✓[a]

a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	Recurrent angina or silent ischaemia	No	3.63 (1.98 to 6.66)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	MI	No	1.18 (0.10 to 13.53)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	Stroke	No	1.18 (0.10 to 13.53)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary bypass surgery	No	1.42 (0.74 to 2.71)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary angioplasty	No	0.93 (0.58 to 2.49)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	CEPI	193 s	SVG patency	Yes	1.00 (0.99 to 1.00)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Collagen/ ADP	88 s	SVG patency	Yes	0.98 (0.97 to 0.99)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Collagen/ ADP	Not clear	SVG patency	Yes	2.82 (1.37 to 5.82)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Bypass surgery or TEA	No	5.29 (0.87 to 32.15)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Peripheral arterial revascularisation	No	2.04 (0.64 to 6.51)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	PTA/stenting	No	0.95 (0.25 to 3.63)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ ADP	Unclear	Stroke	No	0.00 (0.00 to 3.20e+10)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Stroke	No	0.00 (0.00 to 3.20e+10)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Revascularisation	No	0.92 (0.36 to 2.38)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ ADP	Unclear	Revascularisation	No	0.92 (0.36 to 2.38)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	MI	No	1.24 (0.46 to 3.29)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ ADP	Unclear	MI	No	1.24 (0.46 to 3.29)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	CEPI	170 s	Recurrence	No	0.01 (0.00 to 7851.19)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	Collagen/ ADP	120 s	Recurrence	No	0.01 (0.00 to 7851.19)

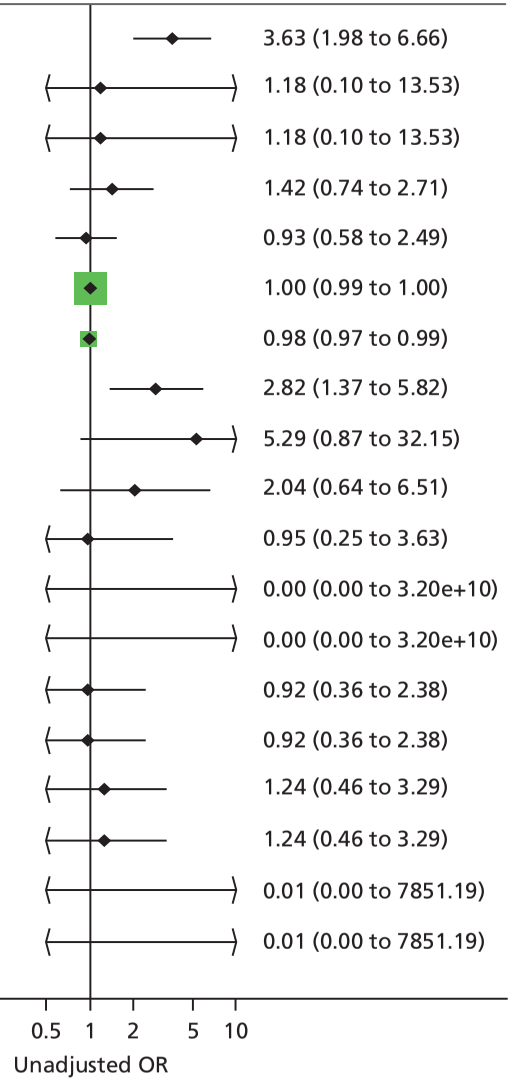

FIGURE 40 PFA-100®, monotherapy: ischaemic/thrombotic events, unadjusted ORs. PTA, percutaneous transluminal angioplasty; s, seconds; TEA, thoracic epidural analgesia.

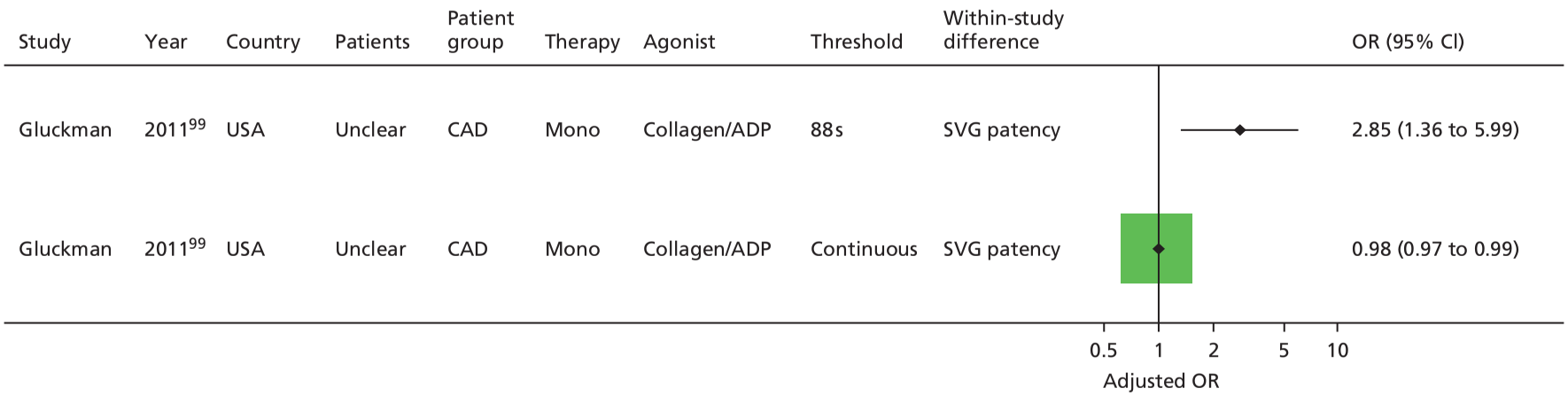

FIGURE 41 PFA-100®, monotherapy: ischaemic/thrombotic events, adjusted ORs. s, seconds.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	MI	No	1.18 (0.11 to 12.96)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	Recurrent angina or silent ischaemia	Yes	2.71 (1.46 to 5.04)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	Stroke	No	1.18 (0.11 to 12.96)
Harrison	2009[189]	UK	620	Miscellaneous	Mono	Collagen/ADP	Not clear	Recurrent ischaemic events	Yes	0.83 (0.60 to 1.15)
Silver	2009[193]	UK	620	Miscellaneous	Mono	CEPI	164 s	Recurrent ischaemic events	Yes	0.83 (0.60 to 1.15)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Bypass surgery or TEA	No	4.77 (0.87 to 26.06)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	PTA/stenting	No	0.96 (0.26 to 3.11)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Peripheral arterial revascularisation	No	1.77 (0.71 to 4.41)
Ziegler	2002[120]	Austria	52	PAD/PVD	Mono	Collagen/ADP	120 s	Recurrence	No	0.01 (0.00 to 8967.45)
Ziegler	2002[120]	Austria	52	PAD/PVD	Mono	CEPI	120 s	Recurrence	No	0.01 (0.00 to 8967.45)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s	CVA	Yes	1.63 (0.72 to 3.67)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s	MI	Yes	3.02 (1.15 to 7.94)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Not clear	MI	No	1.23 (0.48 to 3.13)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	MI	No	1.23 (0.48 to 3.13)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary angioplasty	No	0.96 (0.76 to 1.22)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary bypass surgery	No	1.39 (0.76 to 2.56)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s	Revascularisation	Yes	1.07 (0.51 to 2.24)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Revascularisation	No	0.92 (0.37 to 2.29)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Not clear	Revascularisation	No	0.92 (0.37 to 2.29)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Not clear	Stroke	No	0.00 (0.00 to 3.21e+10)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Stroke	No	0.00 (0.00 to 3.21e+10)

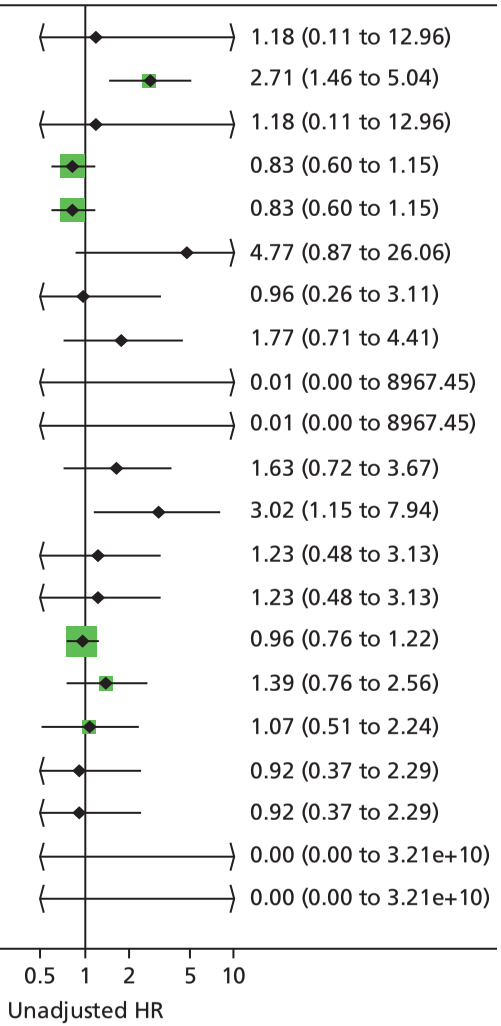

FIGURE 42 PFA-100®, monotherapy: ischaemic/thrombotic events, unadjusted HRs. CVA, cerebrovascular accident; PTA, percutaneous transluminal angioplasty; s, seconds; TEA, thoracic epidural analgesia.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR (95% CI)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	Recurrent angina or silent ischaemia	2.68 (1.35 to 5.32)

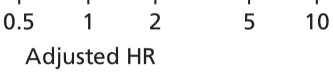

FIGURE 43 PFA-100®, monotherapy: ischaemic/thrombotic events, adjusted HRs. s, seconds.

Bleeding events

One study reported bleeding events (*Table 47*).[144]

No studies were identified that looked at bleeding outcomes over the long term. One study[144] evaluated postoperative bleeding and found that PFA-100® failed to correlate with postoperative bleeding, but PFA-100® measurements repeated immediately after CABG were predictive of blood loss.

Summary: platelet function analyser-100

Twenty-one studies were identified in this category.[76,99,108,109,112,115,116,118,123,127,132,135,137,138,144,145,150,162,186,187,189] There were more populations with stable disease, but those studies with acute populations contributed quite substantially to the results (roughly half of the outcome statistics). There was heterogeneity across studies in terms of specific patient characteristics.

There was a lack of reporting of relevant quality criteria, making overall judgements about risk of bias difficult. No study provided details on all relevant quality criteria. Lack of detail related in particular to whether or not assays were performed in a blinded manner, reporting of compliance levels and, to a lesser extent, whether or not outcome assessors had been blinded to PFT results. In terms of consequences of non-compliance, it appears that in one study[145] patients were excluded on the basis of inadequate salicylate levels, whereas another study[76] did not exclude patients with aspirin non-compliance on the basis that resistance cannot be distinguished from non-compliance. There were a number of methods for deriving the thresholds, which was reflected in the different cut-offs employed (between 150 and 193 seconds where stated, with one study[138] having a much higher threshold at 300 seconds). Some studies provided adjusted results but there was no consistency between studies in terms of factors adjusted for.

Based on 10 studies[76,109,115,118,127,132,135,137,145,186] reporting this outcome, there was an overall trend towards more deaths in the resistant groups, but most results were not statistically significant.

Based on 14 studies,[76,108,109,112,116,118,123,127,132,135,137,138,162,187] there was a mainly consistent trend for MACEs, with more events in the resistant arm, and some results statistically significant. Note that not all studies contributed to the results, particularly the adjusted results. In addition, five of six unadjusted HRs are based on an acute population, which may not be representative of the total population.

TABLE 47 Outcome measures for reporting bleeding events (PFA-100®, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Morawski 2005[144]					Narrative description	

Eleven studies reported additional ischaemic/thrombotic outcomes.[99,109,112,115,118,127,132,135,145,150,189,193] Compared with the large number of unadjusted outcome statistics reported, there were very few adjusted results. The direction of effect was not consistent for these outcomes and there were only a few statistically significant results (with more events in the resistant group). Given the large number of different outcomes and heterogeneity of other factors across studies, it was not possible to compare results for different outcomes (e.g. MI, stroke).

No studies were identified that looked at bleeding outcomes over the long term.

The mainly consistent trend for MACEs and death, with more events in the resistant arm, suggests that PFA-100® is a potential prognostic factor, but this is only a qualitative judgement on the evidence available; the trend for ischaemic/thrombotic events was, however, less consistent. Meta-analysis was not possible owing to the heterogeneity, and therefore a firm quantitative conclusion regarding whether or not PFA-100® is prognostic is not currently possible.

Summary: platelet function analyser-100

- Twenty-one studies were identified for this test.
- There were more stable than acute populations, though studies with acute populations contributed substantially to the results.
- Methods for deriving thresholds and thresholds themselves were variable.
- A lack of detail in reporting of quality criteria, for example whether or not assays were performed in a blinded manner, and in reporting of compliance levels (where measured), hampered an overall risk-of-bias assessment.
- Adjusted results were rarely presented, and thus the additional prognostic value of the test over other prognostic factors is difficult to ascertain.
- There was a mainly consistent trend for MACEs, with more events in the resistant arm, and some statistically significant results; this trend was reflected in studies reporting death, but most results were not statistically significant for this outcome.
- The direction of effect was not consistent for ischaemic/thrombotic events.
- No studies were identified that looked at bleeding outcomes over the long term.
- Not all studies are represented in the forest plots, particularly for the adjusted outcome measures.
- Heterogeneity in outcomes, patient groups and types of reported statistics meant that meta-analysis was not considered appropriate; there is insufficient quantitative information and methodological/clinical homogeneity across studies to enable evidence-based conclusions about the prognostic ability of PFA-100®.

Whole-blood aggregometry

Population and test characteristics

Eight studies[99,117,128,153,162,166,186,196] were identified in this category, two of which were reported in abstract form only.[162,166] Populations had CAD (three studies),[99,117,162] CVD/stroke (two studies),[128,186] PAD/PVD (one study)[153] and UA/ACS where patients were undergoing PPCI (one study).[196] There was one study[166] in patients with end-stage renal disease. Two studies included only patients reporting a first event,[186,196] one study consisted of patients who had suffered previous event(s)[128] and one study reported patients who had their primary underlying condition for a mean period of 41.4 months.[117] Four studies did not report how long patients had been on aspirin therapy.[99,149,166,186]

In seven studies[99,117,128,153,162,166,186] it appeared that patients were exclusively on monotherapy both at the time of the PFT and during follow-up. It is possible that not all studies have reported where a proportion of patients commenced additional therapies during follow-up. In the remaining study,[196] patients were on monotherapy at the time of the PFT and all were on dual therapy (+ clopidogrel or ticlopidine) during a portion of the follow-up period.

Two different methods of WBA were identified across studies and were analysed separately. One study[166] used Multiplate® and seven studies used impedance methodology.[99,117,128,153,162,186,196] Most tests used arachidonic acid or collagen as an agonist, with some also using ADP and epinephrine, and citrate as the anticoagulant (where reported).

Most studies did not report use of other medications. Medications were reported in two studies[99,117] and included statins, beta-blockers, ACE inhibitors, angiotensin receptor blockers, nitrate, lipid-lowering agents, diuretics, digoxin, spironolactone, warfarin, intravenous inotropic therapy and amiodarone. NSAIDs were not permitted (or had to be discontinued within a certain time period) in two studies.[186,196] One study[99] stated that 'concurrent nonsteroidal anti-inflammatory drug use did not correlate with the presence of aspirin non-responsiveness defined by this method at either time point'. There were no details on NSAIDs in the remaining studies.

The number of participants in the studies ranged from 26 to 653 (see *Table 48*). Where reported, mean ages of patients ranged from 52 to 66 years, with most means around the early 60s. There were more men than women in five out of six studies[99,117,128,153,186,196] that reported this, with proportions of men ranging from 52% to 82%. Only one study[128] included more women (55%). The proportion of patients with diabetes ranged from 17% to 44%, and that of smokers from 23% to 69% (where reported) (see *Table 48*). Where reported, studies were conducted in hospital settings.

The dose of aspirin ranged from 75 mg/day to > 325 mg/day. There were no details on dose in one study.[166] Details were variable across studies regarding the length of time patients had been receiving aspirin therapy, with some noting a minimum period and some whether or not patients were chronic users, but many giving no details (see *Table 48*). One study[99] stated that aspirin was provided in enteric form, another reported that aspirin was provided in both enteric and plain forms[117] and the other studies did not report this information.

The main study characteristics are listed in *Table 48*. Note that in some studies baseline characteristics have been reported only according to resistant/sensitive groups, groups with or without diabetes, or groups with occluded or patent SVG during CABG surgery, rather than for the total study population.

Four studies[99,128,162,166] reported no details on the timing of the PFT after aspirin ingestion. Four studies[117,153,186,196] stated that there were up to 24 hours between aspirin dose and the PFT. *Table 49* provides details of test characteristics.

TABLE 48 Population characteristics (WBA, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Multiplate® (MEA) *Monotherapy at time of PFT and during follow-up*										
Orta 2011,[166] Turkey (abstract)	78	No details	Mono	Miscellaneous	No details	No details	No details	No details	43.6	No details
WBA (impedance) *Monotherapy at time of PFT and during follow-up*										
Gengo 2008,[128] USA	653	Resistant ($n = 129$): mean 63.7 Sensitive ($n = 524$): mean 66.5	Mono	CVD/stroke	*Diabetes:* Resistant ($N = 129$): $n = 26$ (20.2%) Sensitive ($N = 524$): $n = 89$ (17%)	No	Various daily doses < 81 mg: 2% 81 mg: 68% 131 mg: 2% 162 mg: 3% 325 mg: 24% > 325 mg: 1%	At least 2 weeks	16.7	Resistance if platelet response, measured in ohms of impedance, > 10 Ω
Gluckman 2011,[99] USA	229	For patients with ≥ 1 occluded SVG ($n = 70$): mean 63 (range 55–72) For patients with patent SVG ($n = 159$): mean 63 (range 57–71)	Mono	CAD	Smokers: $n = 52$ (22.7%) Diabetes: $n = 84$ (36.7%)	Yes: CABG	325 mg/day	No details	No details	Resistant if platelet aggregation > 1 Ω
Lordkipanidzé 2011,[162] UK (abstract)	198	No details	Mono	CAD	No details	No	80–325 mg/day	No details	No details	No details

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Majeed 2009,[117] USA	26	Mean 52.3 (SD 17.1)	Mono	CAD	Smokers: $n = 18$ (69%) Diabetes: $n = 8$ (31%)	Yes	325 mg/day	At least 7 days	96	Aspirin resistance defined as aggregation < 50%
Mueller 1997,[153] Austria	145 (100 eligible for analyses)	Mean 62.5 (SD 11.8)	Mono	PAD/PVD	Smoking history: 57% Diabetes: 31%	Yes: elective percutaneous balloon angioplasty	100 mg/day	All patients stated they had not used any medication containing aspirin for at least the last 14 days prior to the baseline PFT. Aspirin was taken daily prior to follow-up PFT	Decreased platelet function: 35% No change in platelet function: 52%	No details
Sobol 2009,[186] Poland	64 (101 enrolled; 64 stroke patients, 37 controls)	Mean 57.9 (SD 10.4)	Mono	CVD/stroke	Smokers: $n = 24$ (53.3%)	No	150 mg/day	No details	36	Lack of complete inhibition of AA-induced WBA
Monotherapy at time of PFT, dual during follow-up										
Kaminska 2007,[196] Poland	27 (42 total sample; 27 on aspirin, 15 controls)	Diabetes ($n = 12$): mean 61.5 (SD 6.0) Without diabetes ($n = 15$): mean 60.7 (SD 6.7)	Mono (dual during follow-up)	UA/ACS/PPCI	Smokers: 37% Diabetes: $n = 12$ (44.4%)	No details	75–150 mg/day	All patients on aspirin previously. Duration of therapy not stated	18.5	Aspirin resistance was associated with the presence of platelet aggregates induced with AA

AA, arachidonic acid; MEA, multiple electrode aggregometry.

TABLE 49 Test characteristics (WBA, monotherapy)

Study	Details of kit (manufacturer)	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Multiplate® (MEA) *Monotherapy at time of PFT and during follow-up*				
Orta 2011[166] (abstract)	Multiplate® analyser (Dynabyte Medical, Munich, Germany)	No details	No details	No details
WBA (impedance) *Monotherapy at time of PFT and during follow-up*				
Gengo 2008[128]	WBA (Model 700, Chrono-Log Corporation, Havertown, PA, USA)	No details	Collagen (1 µg/ml)	No details
Gluckman 2011[99]	WBA (Model 560CA, Chrono-Log Corporation, Havertown, PA, USA)	3.2% citrate	AA (0.5 mM) ADP (5 µM) ADP (10 µM) ADP (20 µM) Epinephrine (50 µM) Collagen (1 µg/ml)	No details
Lordkipanidzé 2011[162] (abstract)	WBA	No details	AA (1.6 mM)	No details
Majeed 2009[117]	WBA (Whole-Blood Aggregometer®, Chrono-Log Corporation, Havertown, PA, USA)	No details	Collagen (1 µg/ml) Collagen (5 µg/ml)	Up to 24 hours
Mueller 1997[153]	WBA (CHRONO LOG® four-channel whole-blood aggregometer, Chrono-Log Corporation, Havertown, PA, USA)	No details	AA (500 µM) ADP (5 µM) ADP (10 µM) Collagen (2 µg/ml) Collagen (5 µg/ml)	Baseline test: before starting antiplatelet therapy Follow-up tests: up to 24 hours
Sobol 2009[186]	WBA (Chrono-Log, Havertown, PA, USA)	No details	AA (0.5 mM)	Up to 24 hours
Monotherapy at time of PFT, dual during follow-up				
Kaminska 2007[196]	WBA (Chronolog 560, Chrono-Log Corporation, Havertown, PA, USA)	No details	AA (0.125 mM) Collagen (0.5 µg) Collagen (1 µg) Collagen (2 µg)	Up to 24 hours

AA, arachidonic acid; MEA, multiple electrode aggregometry.

Study design and quality

Results of the risk-of-bias assessment can be found in *Tables 50–53*.

Patient selection was independent of study outcome in all included studies, with the PFT preceding any outcomes (as specified in the study selection criteria). Four studies stated that consecutive patients were enrolled into the study[117,128,153,186] and the other studies did not provide details. Only two studies[99,153] had clear details on posteligibility exclusion of patients; in one of these studies[153] a criterion for exclusion was lack of compliance.

TABLE 50 Risk of bias, patient selection (WBA, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Multiplate® (MEA) *Monotherapy at time of PFT and during follow-up*			
Orta 2011[166] (abstract)	No details	Yes	No details
WBA (impedance) *Monotherapy at time of PFT and during follow-up*			
Gengo 2008[128]	Consecutive	Yes	No details
Gluckman 2011[99]	No details	Yes	Patients in whom SVG patency not assessed or those not on aspirin monotherapy. Authors stated that the study population was representative of patients undergoing isolated CABG surgery based on comparison with the Society of Thoracic Surgeons National Database
Lordkipanidzé 2011[162] (abstract)	No details	Yes	No details
Majeed 2009[117]	Consecutive	Yes	No details
Mueller 1997[153]	Consecutive	Yes	45/145 patients initially enrolled and then excluded. Reasons for exclusion: if it could be shown that patients claiming not to have used medication containing aspirin, had been using aspirin; lack of compliance in correct usage of aspirin; other exclusion criteria. All exclusion criteria seem to have been applied after enrolment and consent
Sobol 2009[186]	Consecutive	Yes	No details
Monotherapy at time of PFT, dual during follow-up			
Kaminska 2007[196]	No details	Yes	No details

MEA, multiple electrode aggregometry.

TABLE 51 Risk of bias, PFT (WBA, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Multiplate® (MEA)			
Monotherapy at time of PFT and during follow-up			
Orta 2011[166] (abstract)	No details	No details	No details
WBA (impedance)			
Monotherapy at time of PFT and during follow-up			
Gengo 2008[128]	Yes (patients considered to be non-responsive to aspirin if their platelet response, measured in ohms of impedance, to 1 µg/ml of collagen was > 10 Ω, > 50% of their response to 5 µg/ml of collagen and/or > 6 Ω to 0.5 mM AA)	Criteria similar to ones cited (references given[226–230])	No details (but quality control procedures described)
Gluckman 2011[99]	Yes (aspirin resistant if AA-induced platelet aggregation was > 1 Ω)	Stated that normal range in authors' laboratory for aspirin-naive subjects was 5–7 Ω. No further details	No details
Lordkipanidzé 2011[162] (abstract)	No details	No details	No details
Majeed 2009[117]	Yes (aspirin resistance defined as at least 50% platelet response)	Formula and reference cited[231]	No details
Mueller 1997[153]	No threshold	Different 'classes' of effect of aspirin on platelet function depending on change from baseline derived from data	No details
Sobol 2009[186]	Yes (but no numerical cut-off)	A lack of complete inhibition of AA-induced whole-blood aggregation	No details
Monotherapy at time of PFT, dual during follow-up			
Kaminska 2007[196]	Not explicitly stated; assumed that if there is any aggregation patients are classed as aspirin resistant	No details	No details

AA, arachidonic acid; MEA, multiple electrode aggregometry.

TABLE 52 Risk of bias, outcomes and study attrition (WBA, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Multiplate® (MEA)			
Monotherapy at time of PFT and during follow-up			
Orta 2011[166] (abstract)	Yes	No details	Appears to be no loss to follow-up
WBA (impedance)			
Monotherapy at time of PFT and during follow-up			
Gengo 2008[128]	Yes	No details	Appears to be no loss to follow-up
Gluckman 2011[99]	Yes	Yes. Stated that images were analysed by two blinded reviewers (98% concordance) with a third reviewer adjudicating as necessary	75/229 patients not included at follow-up
Lordkipanidzé 2011[162] (abstract)	Yes	No details	No details
Majeed 2009[117]	Yes	No details	No losses to follow-up
Mueller 1997[153]	Yes	No details	4/100 patients lost to follow-up by 52 weeks (for repeat PFT) but appears all patients included for outcomes
Sobol 2009[186]	Yes	No details	No losses to follow-up
Monotherapy at time of PFT, dual during follow-up			
Kaminska 2007[196]	No; the paper did not focus on clinical outcomes (it was focused on the results of the PFTs)	Yes	The paper states that one person (out of 27) was lost to follow-up at 6 months as a result of MI; this is the same person who is recorded as having the clinical event of MI

MEA, multiple electrode aggregometry.

TABLE 53 Risk of bias, confounders (WBA, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Multiplate® (MEA) *Monotherapy at time of PFT and during follow-up*						
Orta 2011[166] (abstract)	Design: N/A Analysis: no	N/A	No details	No details	No details	No details
WBA (impedance) *Monotherapy at time of PFT and during follow-up*						
Gengo 2008[128]	Design: N/A Analysis: yes (OR)	Age and sex; diseases including diabetes, hypertension, dyslipidaemia and CAD; nature of recurrent event (stroke vs. TIA); and the use of other drugs (clopidogrel, dipyridamole, COX-2 selective non-steroidal anti-inflammatory agents, non-selective anti-inflammatory agents)	N/A	Yes	Method described for determining presence of salicylates in urine. Patients without salicylates in their urine were excluded at baseline	No details
Gluckman 2011[99]	Design: N/A Analysis: no	N/A	N/A	Yes	Pill counts at each postoperative encounter	No details
Lordkipanidzé 2011[162] (abstract)	Design: N/A Analysis: unclear whether adjusted or unadjusted OR	No details	N/A	No details	No details	No details

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Majeed 2009[117]	Design: N/A Analysis: no	N/A	N/A	Yes	Daily aspirin administration in hospital confirmed by patients' self-reporting, reports from nursing personnel and reviews of daily pharmacy records. After discharge, adherence to daily aspirin was assessed at each weekly visit by verbal self-reporting from patients	No details
Mueller 1997[153]	Design: N/A Analysis: no	N/A	N/A	Yes	A positive reaction to AA-mediated aggregometry. Non-compliance resulted in exclusion from the study	No details
Sobol 2009[186]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Monotherapy at time of PFT, dual during follow-up						
Kaminska 2007[196]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details

AA, arachidonic acid; MEA, multiple electrode aggregometry; N/A, not applicable.

A predetermined threshold percentage (for platelet aggregation) was given in four studies.[99,117,128,186] Thresholds were > 1 Ω[99] at least 50% platelet response;[117] and > 10 Ω in response to 1 μg/ml of collagen, > 50% of the response to 5 μg/ml of collagen and/or > 6 Ω to 0.5 mM arachidonic acid.[128] In one study the numerical cut-off was not stated and patients were described as resistant if there was a 'lack of complete inhibition of arachidonic acid induced whole blood aggregation'.[186] Another study[196] stated that patients were classed as aspirin resistant if there was any aggregation at all. One study stated that quartiles were used,[153] and the remaining two studies[162,166] reported no details. None of the studies gave clear details on blinding of laboratory staff to patient characteristics.

Outcome measures of interest were clearly predefined in all but one study.[99,117,128,153,162,166,186] None of the studies provided clear details regarding blinding to the PFT results of those assessing outcomes.

There appeared to be no loss to follow-up in four studies.[117,128,166,186] Loss to follow-up was stated in two studies[153,196] and was approximately 4% in both. There were no clear details in one study.[162] The differences in completeness of follow-up may reflect length of follow-up, study design (outcome only followed up in those that had repeat PFTs) or quality of reporting.

Compliance was measured in four studies,[99,117,128,153] but there were no details on level of compliance. It was determined by presence of salicylates in urine,[128] pill counts,[99] patient interview, nurse assessment and pharmacy records during the period of hospitalisation and through self-report only after discharge,[117] and a positive reaction to arachidonic acid-mediated aggregometry.[153] The four remaining studies reported no details on compliance.[162,166,186,196]

Six studies did not appear to undertake any adjusted analyses.[99,117,153,166,186,196] One study[128] attempted to adjust for a number of factors, including age, sex, presence of various comorbidities, nature of recurrent event and use of various other drugs. In one study[162] it is not clear whether the ORs reported were adjusted or unadjusted. There may be selective reporting in that only variables that showed significance on univariate analysis might have been included in multivariate analyses.

Overview of outcomes

There were eight studies[99,117,128,153,162,166,186,196] using WBA as a PFT and reporting on death, MACEs and ischaemic/thrombotic events (*Table 54*).

Death

Two studies[186,196] reported deaths (*Table 55*). One of these[186] could not be presented in a forest plot, as although it stated that one death occurred in the resistant group, it was unclear whether resistance was determined by WBA and/or PFA-100®. Outcome statistics are presented in *Figures 44* and *45*. Unadjusted ORs and HRs were calculable for the other study.[196] These were not statistically significant; the wide CIs reflect the fact that there were two events in the resistant arm and no events in the sensitive arm.

Though the trend across the two studies is consistent (the only events are in the resistant group), there were too few studies and events to draw any conclusion regarding risk of death.

TABLE 54 Studies and outcomes (WBA, monotherapy)

Study	Death	MACEs	Ischaemic/ thrombotic events	Bleeding	Length of follow-up
Multiplate® (MEA)					
Monotherapy at time of PFT and during follow-up					
Orta 2011[166] (abstract)		✓			Mean 20.7 months (SD 6.1 months)
WBA (impedance)					
Monotherapy at time of PFT and during follow-up					
Gengo 2008[128]			✓		29 months
Gluckman 2011[99]			✓		6 months
Lordkipanidzé 2011[162] (abstract)		✓			3 years
Majeed 2009[117]			✓		Median 315 days (range 9–833 days)
Mueller 1997[153]			✓		18 months
Sobol 2009[186]	✓				10 days
Monotherapy at time of PFT, dual during follow-up					
Kaminska 2007[196]	✓		✓		12 months

MEA, multiple electrode aggregometry.

TABLE 55 Outcome measures for reporting death (WBA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
WBA (impedance)						
Monotherapy at time of PFT and during follow-up						
Sobol 2009[186]					Unclear which test used to classify as resistant	
Monotherapy at time of PFT, dual during follow-up						
Kaminska 2007[196]	✓[a]		✓[a]			✓[a]

a Calculated from data given in the publication.

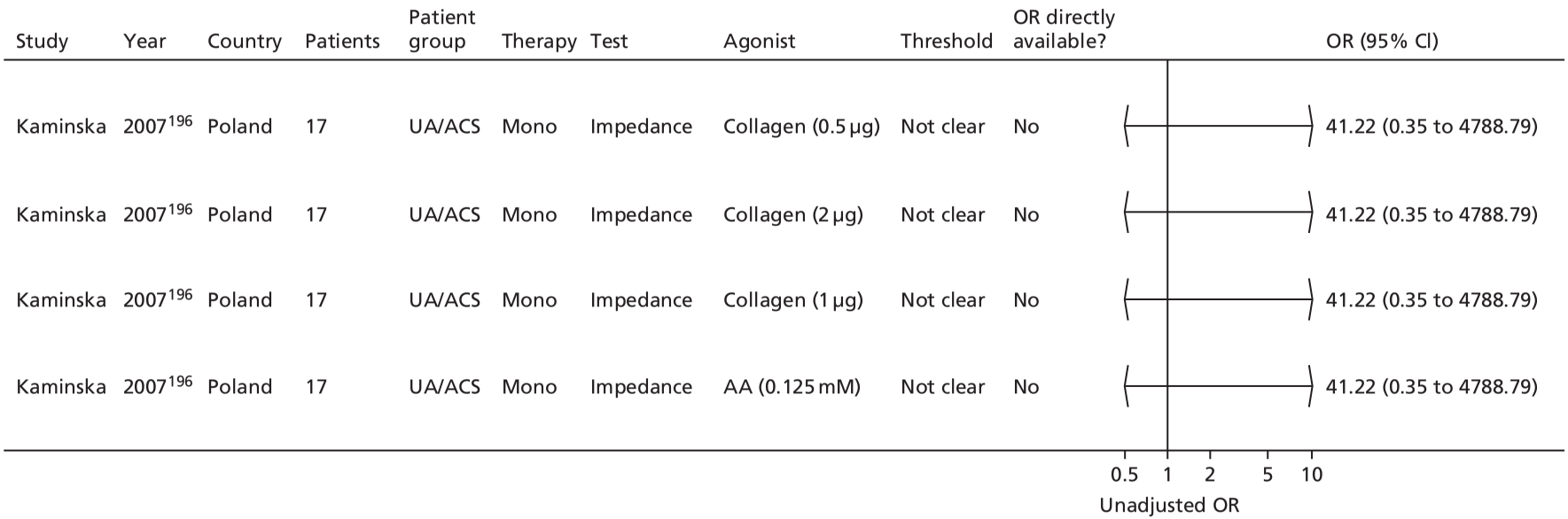

FIGURE 44 Whole-blood aggregometry, monotherapy: death, unadjusted ORs. AA, arachidonic acid.

FIGURE 45 Whole-blood aggregometry, monotherapy: death, unadjusted HRs. AA, arachidonic acid.

Major adverse cardiac events

Two studies reported MACEs[162,166] (*Table 56*). Outcome statistics are shown in *Figures 46* and *47*. One study,[162] in a CAD population, reported a non-statistically significant unadjusted OR. The other study[166] reported an unadjusted OR and HR, which were both statistically significant. It should be noted that, although considered to be at cardiovascular risk, this was primarily a renal failure population, which might not be comparable with the other studies included here. This study also used the Multiplate® system.

Based on these two studies, no conclusions can be drawn regarding the risk of MACEs.

TABLE 56 Outcome measures for reporting MACEs (WBA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Multiplate® (MEA) *Monotherapy at time of PFT and during follow-up*						
Orta 2011[166] (abstract)	✓[a]		✓			✓[a]
WBA (impedance) *Monotherapy at time of PFT and during follow-up*						
Lordkipanidzé 2011[162] (abstract)	✓[a]					

MEA, multiple electrode aggregometry.
a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	OR directly available?	OR (95% CI)
Lordkipanidzé	2011[162]	Canada	Unclear	CAD	Mono	Impedance	AA (1.6 mM)	No details	Yes	1.10 (0.34 to 3.59)
Orta	2011[166]	Turkey	78	Miscellaneous	Mono	Impedance	Not stated	Not stated	No	3.27 (1.13 to 9.48)

FIGURE 46 Whole-blood aggregometry, monotherapy: MACEs, unadjusted ORs. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	OR directly available?	HR (95% CI)
Orta	2011[166]	Turkey	78	Miscellaneous	Mono	Multiplate	Not stated	Not stated	Yes	2.72 (1.07 to 6.94)

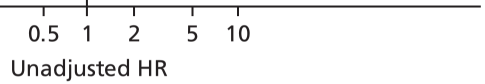

FIGURE 47 Whole-blood aggregometry, monotherapy: MACEs, unadjusted HRs.

Ischaemic/thrombotic events

Five studies[99,117,128,153,196] reported ischaemic/thrombotic outcomes (*Table 57*). Results from two[117,153] of these could not be presented in a forest plot. In one[117] it appeared that all eight thromboembolic events occurred in the resistant arm, but overall numbers of patients in the resistant and sensitive groups were unclear. In the other study,[153] no patients were defined as resistant and therefore all eight events (reocclusions) occurred in sensitive patients.

Outcome statistics are presented in *Figures 48–50*. Eleven unadjusted ORs were presented based on three studies.[99,128,196] There was only one event (MI) in one study,[196] therefore the four ORs are associated with very wide CIs. One study[99] finds no difference in risk, whereas in one[128] the ORs are statistically significant (more events in the resistant arm).

These ORs remain statistically significant when adjusted for. Unadjusted HRs are also statistically significant for the same study,[128] but not for the other study[196] presenting unadjusted HRs.

Given the heterogeneity between studies (population, outcomes) and the lack of consistency in terms of direction of effect, no firm conclusions can be drawn.

Summary: whole-blood aggregometry

Eight studies were identified,[99,117,128,153,162,166,186,196] with mainly stable disease populations (seven of eight studies). In one study[196] with an acute disease population, dual therapy was initiated after the PFT. Only one[166] of the eight studies used the Multiplate® system.

There was a lack of reporting of quality criteria, making overall judgements about risk of bias difficult. Lack of detail related to blinding in particular (to patient characteristics and results of the PFT) and the level of compliance. Only two studies[99,153] gave details on posteligibility exclusions and only three studies[99,117,128] gave details on the threshold used.

Only two studies reported deaths,[186,196] with a total of three events across both studies. There are therefore too few data to draw any firm conclusions on the risk of death. MACEs were also only reported by two studies.[162,166] A statistically significant result (more events in the resistant arm) was shown by one of these,[166]

TABLE 57 Outcome measures for reporting ischaemic/thrombotic events (WBA, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
WBA (impedance)						
Monotherapy at time of PFT and during follow-up						
Gengo 2008[128]	✓[a]	✓	✓[a]			✓[a]
Gluckman 2011[99]	✓					
Majeed 2009[117]					Proportions of patients in resistant and sensitive groups were unclear	
Mueller 1997[153]					No patients defined as resistant	
Monotherapy at time of PFT, dual during follow-up						
Kaminska 2007[196]	✓[a]		✓[a]			✓[a]

a Calculated from data given in the publication.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Impedance	ADP (20 µM)	Not clear	SVG patency	Yes	0.98 (0.92 to 1.05)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Impedance	ADP (5 µM)	Not clear	SVG patency	Yes	1.06 (0.91 to 1.24)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Impedance	Collagen (1 µg)	Not clear	SVG patency	Yes	1.00 (0.93 to 1.06)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Impedance	ADP (10 µM)	Not clear	SVG patency	Yes	1.10 (0.66 to 1.84)
Gluckman	2011[99]	USA	Unclear	CAD	Mono	Impedance	Epinephrine (50 µM)	Not clear	SVG patency	Yes	1.01 (0.96 to 1.06)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	AA (0.5 mM)	6 Ω	Cerebral ischemic event	No	4.85 (2.89 to 8.12)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	Collagen (1 µg)	10 Ω	Cerebral ischemic event	No	10.19 (6.19 to 16.78)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (0.5 µg)	Not clear	MI	No	16.18 (0.12 to 2173.06)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	AA (0.125 µM)	Not clear	MI	No	16.18 (0.12 to 2173.06)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (2 µg)	Not clear	MI	No	16.18 (0.12 to 2173.06)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (1 µg)	Not clear	MI	No	16.18 (0.12 to 2173.06)

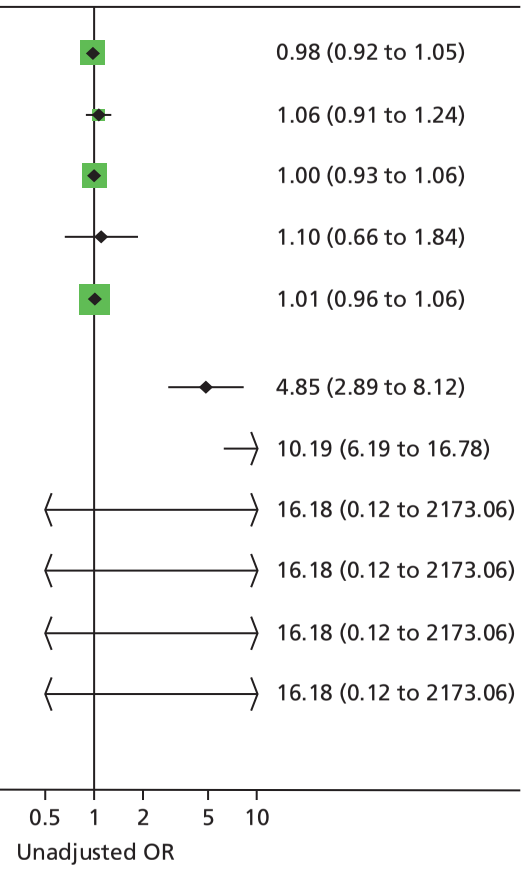

FIGURE 48 Whole-blood aggregometry, monotherapy: ischaemic/thrombotic events, unadjusted ORs. AA, arachidonic acid.

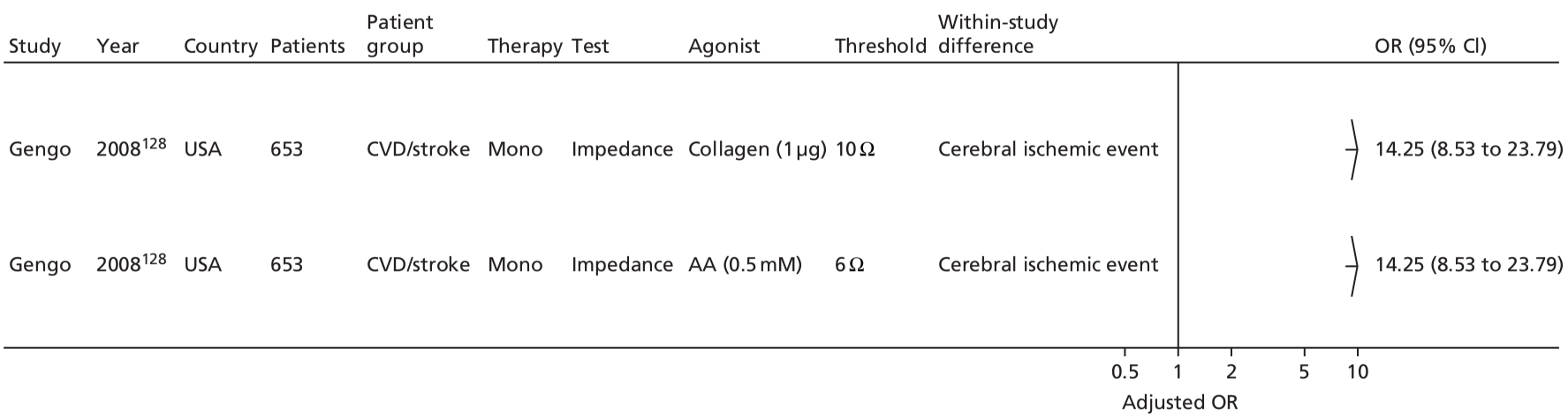

FIGURE 49 Whole-blood aggregometry, monotherapy: ischaemic/thrombotic events, adjusted ORs. AA, arachidonic acid.

FIGURE 50 Whole-blood aggregometry, monotherapy: ischaemic/thrombotic events, unadjusted HRs. AA, arachidonic acid.

and again, firm conclusion cannot be drawn, particularly as there were differences in populations between the studies and differences in test characteristics. More data were available for ischaemic/thrombotic events, based on five studies.[99,117,128,153,196] However, there were differences in populations (e.g. CAD, UA/ACS), outcome measures (e.g. SVG patency, MI, reocclusion, cerebral ischaemic events) and treatment (e.g. dual therapy after the PFT), and there appeared to be little consistency across results, though some were statistically significant (more events in the resistant arm). There were no studies reporting bleeding events.

Given the above data it is difficult to assess the overall prognostic effect, and no conclusions can be drawn regarding the overall potential usefulness of WBA as a prognostic factor.

Summary: whole-blood aggregometry

- Eight studies were identified, with patients with stable disease in seven of these.
- The PFT thresholds used were not always reported or consistent across studies.
- A lack of detail in reporting of quality criteria, particularly around blinding and details (and implications) of compliance, hampered an overall risk-of-bias assessment.
- Heterogeneity in outcomes, patient groups and types of reported statistics meant that meta-analysis was not possible.
- Few adjusted results were presented, and thus it is not possible to ascertain the additional prognostic value of the test over other prognostic factors.
- Given the limited number of data, no firm conclusions could be drawn regarding risk of death or MACEs.
- Heterogeneity around populations, outcomes and treatment (post PFT), and a lack of a clear consistent trend across the studies, meant that firm conclusions could also not be drawn for ischaemic/thrombotic events, though there were some statistically significant results (more events in the resistant arm).
- No studies reported bleeding events.

Thromboelastography

Population and test characteristics

Three studies[117,168,174] were identified in this category, two of which were reported in abstract form only.[168,174] Populations had CAD (two studies)[117,168] and UA/ACS (one study).[174] One study[117] reported that patients had their primary underlying condition for a mean period of 41.4 months. The two remaining studies did not report this information.

In all three studies,[117,168,174] it appeared that patients were exclusively on monotherapy both at the time of the PFT and during follow-up. It is possible that not all studies have reported where a proportion of patients commenced additional therapies during follow-up.

Only one study[117] reported medications used by patients. These included diuretics, ACE inhibitors, angiotensin II receptor blockers, beta-blockers, digoxin, spironolactone, nitrate, statins, warfarin, intravenous inotropic therapy and amiodarone. None of the studies reported details on NSAIDs.

The number of participants in the studies ranged from 26 to 250 (see *Table 58*). Mean ages of patients were 52,[117] 60[168] and 62 years.[174] There were more men than women in two studies,[117,168] with proportions of 73%[117] and 68.5%.[168] The remaining study[174] reported sex data for aspirin-resistant patients only (42 of the total sample of 250), 74% of whom were male.

The dose of aspirin was reported in all studies and ranged from 15 mg/day to 325 mg/day. Two studies[168,174] gave no details regarding the length of time patients had been receiving aspirin therapy, and one study reported that patients had been taking aspirin for at least 7 days[117] (see *Table 58*). One study[117] reported that aspirin was provided in both enteric and plain forms, and the other studies did not report this information.

The main study characteristics are listed in *Table 58*.

TABLE 58 Population characteristics (TEG, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/comment
Monotherapy at time of PFT and during follow-up										
Majeed 2009,[117] USA	26	Mean 52.3 (SD 17.1)	Mono	CAD	Smokers: $n = 18$ (69%) Diabetes: $n = 8$ (31%)	Yes	325 mg/day	At least 7 days	96	Aspirin resistance defined as aggregation ≥ 50%
Sahin 2011,[168] Turkey (abstract)	168	Mean 60.1 (SD 8.4)	Mono	CAD	No details	No details	100 mg/day	No details	16.1	Aspirin resistance defined as aggregation ≥ 50%
Tan 2010,[174] China (abstract)	250	Mean 62 (SD 17)	Mono	UA/ACS	No details	No details	15–250 mg/day	No details	18.8	Aspirin resistance defined as aggregation ≥ 50%

The test performed in all studies was TEG. All studies used arachidonic acid as an agonist and details regarding anticoagulants were not reported in any studies.

Two studies[117,174] stated that there were up to 24 hours between aspirin dose and PFT. The remaining study[168] provided no details on the time between taking aspirin and the PFT. *Table 59* provides details of test characteristics.

Study design and quality

Results of the risk-of-bias assessment can be found in *Tables 60–63*.

Patient selection was independent of study outcome in all three included studies,[117,168,174] with the PFT preceding any outcomes (as specified in the study selection criteria). All studies stated that consecutive patients were enrolled into the study and no studies had clear details on posteligibility exclusion of patients.

A predetermined threshold percentage (for platelet aggregation) was given as > 50% or ≥ 50% for all three studies.[117,168,174] Only one study[117] cited a reference[232] and provided details on the method of derivation of this threshold. For the remaining two studies there were no details on threshold derivation. None of the studies gave clear details on blinding of laboratory staff to patient characteristics.

Outcome measures of interest were clearly predefined in two studies.[117,174] In one of these studies it was unclear if outcomes were separate or composite,[174] and the remaining study provided no details. None of the studies had clear details regarding blinding to the PFT results of those assessing outcomes. There appeared to be no loss to follow-up in two studies[117,168] and the remaining study[174] provided no details on missing data or whether or not there was any loss to follow-up.

Compliance was measured in one study[117] by patient interview, nurse assessment and pharmacy records during the period of hospitalisation, and through self-report only after discharge. No details on the level of compliance were stated.

All three studies did not appear to undertake any adjusted analyses.

TABLE 59 Test characteristics (TEG, monotherapy)

Study	Details of kit (manufacturer)	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Monotherapy at time of PFT and during follow-up				
Majeed 2009[117]	TEG® 5000 (Thromboelastograph® Hemostasis Analyzer, Haemonetics Corporation, Braintree, MA)	No details	Collagen (1 µg/ml) Collagen (5 µg/ml)	Up to 24 hours
Sahin 2011[168] (abstract)	Modified thromboelastogram	No details	AA	No details
Tan 2010[174] (abstract)	TEG® (Haemonetics Corporation, Braintree, MA)	No details	AA	Up to 24 hours

AA, arachidonic acid.

TABLE 60 Risk of bias, patient selection (TEG, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Monotherapy at time of PFT and during follow-up			
Majeed 2009[117]	Consecutive	Yes	No details
Sahin 2011[168] (abstract)	Consecutive	Yes	No details
Tan 2010[174] (abstract)	Consecutive	Yes	No details

TABLE 61 Risk of bias, PFT (TEG, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Monotherapy at time of PFT and during follow-up			
Majeed 2009[117]	Yes (≥ 50%)	Formula and reference cited[232]	No details
Sahin 2011[168] (abstract)	Yes (< 50% AA-induced whole-blood thrombosit aggregation inhibition by TEG)	No details	No details
Tan 2010[174] (abstract)	Yes (> 50%)	No details	No details

AA, arachidonic acid.

TABLE 62 Risk of bias, outcomes and study attrition (TEG, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Monotherapy at time of PFT and during follow-up			
Majeed 2009[117]	Yes	No details	No losses to follow-up
Sahin 2011[168] (abstract)	No details	No details	No losses to follow-up
Tan 2010[174] (abstract)	Yes (although unclear if separate or composite)	No details	No details

TABLE 63 Risk of bias, confounders (TEG, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Monotherapy at time of PFT and during follow-up						
Majeed 2009[117]	Design: N/A Analysis: no	N/A	N/A	Yes	Daily aspirin administration in hospital confirmed by patients' self-reporting, reports from nursing personnel and reviews of daily pharmacy records. After discharge, adherence to daily aspirin was assessed at each weekly visit by verbal self-reporting from patients	No details
Sahin 2011[168] (abstract)	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Tan 2010[174] (abstract)	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details

N/A, not applicable.

Overview of outcomes

Three studies were identified,[117,168,174] reporting on only two of the outcomes of interest (death and ischaemic/thrombotic events) (*Table 64*).

Death

Two studies reported on deaths (*Table 65*).[168,174] One study was not presented in the forest plots.[174] This found a death rate of 26% in the resistant group and 11% in the sensitive group (UA/ACS population), but there were no raw data to confirm these proportions. Outcome statistics are presented in *Figures 51* and *52*. In the other study, both the adjusted OR and HR were statistically non-significant. The wide CI reflects the fact that there was only one death in the resistant group and no deaths in the sensitive group.

Overall, there is too little evidence on which to base any conclusions regarding risk of death.

TABLE 64 Outcomes (TEG, monotherapy)

Study	Death	MACEs	Ischaemic/thrombotic events	Bleeding	Length of follow-up
Monotherapy at time of PFT and during follow-up					
Majeed 2009[117]			✓		Median 315 days (range 9–833 days)
Sahin 2011[168] (abstract)	✓		✓		Mean 464 days (SD 264 days)
Tan 2010[174] (abstract)	✓		✓		360 days (range 0–523 days); not stated if mean or median

TABLE 65 Outcome measures for reporting death (TEG, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Sahin 2011[168] (abstract)	✓[a]		✓[a]			✓[a]
Tan 2010[174] (abstract)						

a Calculated from data given in the publication.

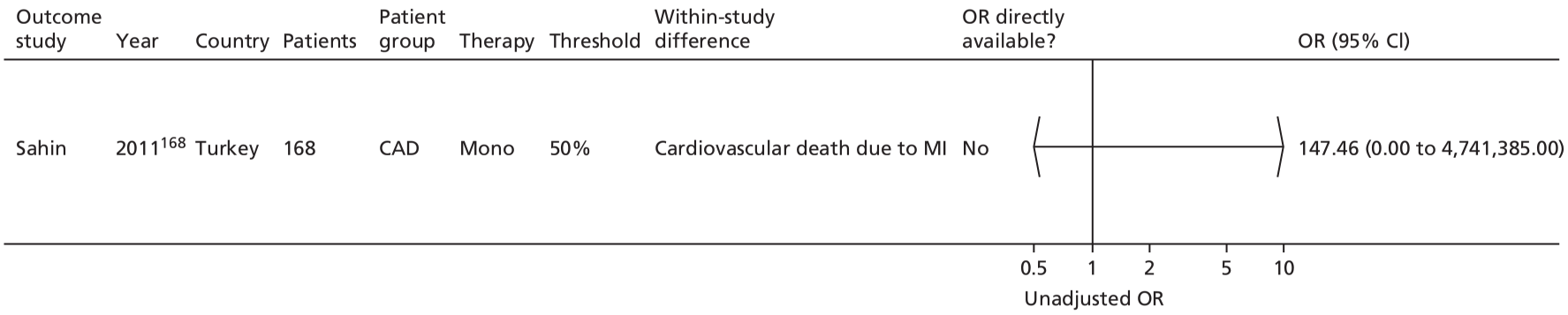

FIGURE 51 Thromboelastography, monotherapy: death, unadjusted ORs.

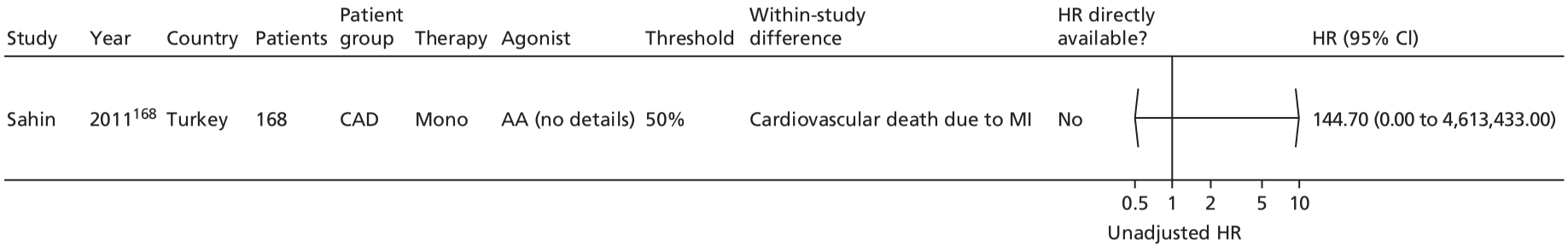

FIGURE 52 Thromboelastography, monotherapy: death, unadjusted HRs. AA, arachidonic acid.

Ischaemic/thrombotic events

Three studies reported ischaemic/thrombotic events (*Table 66*).[117,168,174] Two of these were not presented in the forest plots. One[174] found a rate of 74% in the resistant group for recurrent MI or thrombosis and 24% in the sensitive group (UA/ACS population), but there were no raw data to confirm these proportions. In the other study,[117] it appeared that all eight thromboembolic events occurred in the aspirin-resistant group.

Outcome statistics are presented in *Figures 53* and *54*. Unadjusted ORs and HRs of the third study[168] were all statistically significant for different outcomes.

Thus, it appears that more events occurred consistently in the resistant arm; however, this is based on only three studies,[117,168,174] two of which[117,174] did not report all relevant data clearly.

Summary: thromboelastography

Only three studies were identified in this category,[117,168,174] two with a stable[117,168] and one with an acute[174] disease population. Two of the three were in abstract form,[168,174] so there is a lack of detail on specific patient characteristics.

There was a lack of detail in reporting of quality criteria, making overall judgements about risk of bias difficult. Lack of detail related in particular to blinding and level of compliance. The same threshold was used across the three studies. No adjusted outcome statistics were reported.

TABLE 66 Outcome measures for reporting ischaemic/thrombotic events (TEG, monotherapy)

Study	Unadjusted OR	Adjusted OR	Unadjusted HR	Adjusted HR	Other measures related to prognosis	Sensitivity/specificity presented or calculable
Monotherapy at time of PFT and during follow-up						
Majeed 2009[117]						
Sahin 2011[168] (abstract)	✓[a]		✓[a]			✓[a]
Tan 2010[174] (abstract)						

a Calculated from data given in the publication.

Outcome study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	OR directly available?	OR (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	ACS with hospitalisation	No	5.11 (1.44 to 18.20)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Recurrent interventional treatment	No	5.47 (1.67 to 17.86)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Primary outcome events (ACS, death, recurrent treatment)	No	7.88 (3.05 to 20.36)

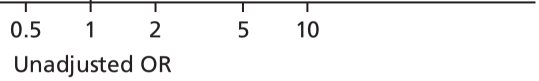

FIGURE 53 Thromboelastography, monotherapy: ischaemic/thrombotic events, unadjusted ORs.

Outcome study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	HR directly available?	HR (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	AA (no details)	50%	ACS with hospitalisation	No	4.71 (1.44 to 15.43)
Sahin	2011[168]	Turkey	168	CAD	Mono	AA (no details)	50%	Primary outcome events (ACS, death, recurrent treament)	No	6.08 (2.77 to 13.32)
Sahin	2011[168]	Turkey	168	CAD	Mono	AA (no details)	50%	Recurrent interventional treament	No	4.94 (1.66 to 14.69)

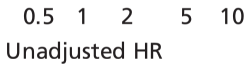

FIGURE 54 Thromboelastography, monotherapy: ischaemic/thrombotic events, unadjusted HRs. AA, arachidonic acid.

Two studies reported deaths[168,174] and three reported ischaemic/thrombotic events. Only one study for each outcome could be presented in a forest plot.[168] There was too little evidence to draw any conclusions for risk of death. The direction of effect was consistent for ischaemic/thrombotic events (more events in the resistant group), but this was based on few studies and there were some reporting issues. There were differences in study populations and types of outcome measures reported (for ischaemic/thrombotic events). No adjusted measures were reported and there were no studies reporting MACEs or bleeding events.

Despite the heterogeneity, the direction of prognostic effect appears to be largely consistent with more events occurring in aspirin-resistant patients (ORs and HRs usually > 1). This suggests that TEG is a potential prognostic factor, but this is only a qualitative judgement on the evidence available and is based on very few studies; meta-analysis was not possible as there was only one study in the forest plots, and therefore a firm quantitative conclusion regarding whether or not TEG is prognostic is not currently possible.

Summary: thromboelastography

- Three studies were identified (two with stable, one with an acute disease population).
- The threshold used was consistent (50%).
- A lack of detail in reporting of quality criteria, particularly around blinding and details (and implications) of compliance, hampered an overall risk-of-bias assessment.
- Heterogeneity in outcomes, patient groups and types of reported statistics, and the fact that only one study presented data suitable for use in a forest plot, meant that meta-analysis was not possible.
- No adjusted results were presented, and thus it is not possible to ascertain the additional prognostic value of the test over other prognostic factors.
- No conclusions could be drawn regarding risk of death in resistant and sensitive groups.
- Despite clinical heterogeneity between studies, there was an overall consistent trend for more events to occur in the 'aspirin-resistant' group for ischaemic/thrombotic events; however, this was based on one study only.
- No studies reported MACEs or bleeding events.

Miscellaneous tests

The population and test characteristics are presented in *Tables 67* and *68*. There was a large amount of heterogeneity across the studies in terms of PFTs and populations. No two studies used both the same PFT and the same treatment after the PFT (i.e. monotherapy or dual therapy; see *Table 67*), therefore each study needs to be considered on its own.

TABLE 67 Population characteristics (other, monotherapy)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Monotherapy at time of PFT and during follow-up										
Flow cytometry										
Frelinger 2009,[76] USA	700 (555 eligible for analysis)	Mean 60.7 (SEM 0.44)	Mono (32% dual during follow-up)	CAD	Smokers: 22% current (72% prior) Diabetes: 27%	No	81 or 325 mg/day	At least 3 days	8.1	No details
Monotherapy at time of PFT, dual during follow-up										
Flow cytometry										
Kaminska 2007,[196] Poland	27 (42 total sample; 27 on aspirin, 15 controls)	With diabetes ($n = 12$): mean 61.5 (SD 6.0) Without diabetes ($n = 15$): mean 60.7 (SD 6.7)	Mono (dual during follow-up)	UA/ACS/ PPCI	Smokers: 37% Diabetes: $n = 12$ (44.4%)	No details	75–150 mg/ day	All patients on aspirin previously. Duration of therapy not stated	18.5	Aspirin resistance was associated with presence of platelet aggregates with blood induced with AA
Surgicutt II										
Buchanan 2000,[152] Canada	516 (289 eligible for analysis)	Resistant ($n = 158$): mean 60.8 (SD 9.3) Sensitive ($n = 131$): mean 61.4 (SD 8.8)	Mono	CABG	Ex-smokers: 63.1% of resistant group ($n = 158$); 78.8% of sensitive group ($n = 131$) Diabetes: 19.6% of resistant group ($n = 158$); 20.6% of sensitive group ($n = 131$)	No details	325 mg/day	2 weeks. Bleeding times also recorded when not taking aspirin for at least 1 week	54.7	Coefficient of variation between on and off aspirin bleeding times ≤ 26% classified as aspirin resistant

continued

TABLE 67 Population characteristics (other, monotherapy) (*continued*)

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Apact II platelet aggregometer										
Stejskal 2006,[198] Czech Republic	103	64 (SD 13)	Mono	ACS	Smokers: 21% active or past smokers Diabetes: 33%	No details	100 mg/day	At least 3 days	55.3	Aspirin resistant if spontaneous aggregation was > 5% and if the slope of the aggregation curve after CPG induction was above 53%/minute
Platelet reactivity test										
Grotemeyer 1993,[154] Germany	180 (174 eligible for analysis)	Mean 58 (SD 15)	Mono	CVD/stroke	76 patients (7 who subsequently had an event, 69 who did not have an event)	No details	500 mg three times a day	24 months	34.5	Platelet reactivity value > 1.25
Impact-R® (cone and platelet analyser test) *Monotherapy at time of PFT and during follow-up*										
Schwammenthal 2008,[125] Israel	105 (79 eligible for analysis)	Mean 63 (SD 12)	Mono (3.8% on dual at baseline and follow-up)	CVD/stroke	Current smokers: $n = 20$ (19%) Past smokers: $n = 9$ (27.6%) Diabetes: $n = 28$ (26.7%)	No	100 mg/day (55%), 325 mg/day (45%)	After stroke onset (at least 6 hours prior to PFT). 40% on chronic aspirin therapy (> 1 week prior to stroke)	46.8	Partial response 20–39% aggregation, good response < 20% aggregation

Study/country	Number of patients	Age (years)	Therapy	Main underlying condition	Selected other population details	Due to undergo vascular intervention?	Aspirin dose/ frequency	Duration of aspirin therapy (prior to PFT)	Percentage aspirin resistant	Derivation of threshold/ comment
Monotherapy at time of PFT, dual during follow-up										
Spectre 2011,[93] Israel	63 (54 eligible for analysis)	Mean 59.7	Mono at time of PFT (dual during follow-up, post PCI)	PPCI	Smokers: 30% Diabetes: 24%	Yes	100 mg/day	Previous long-term aspirin use in 73%	66.7	Percentage surface coverage of adherent platelets. Upper tertile 1.95 (SEM 0.35), middle tertile 1.24 (SEM 0.1), lower tertile 3.3 (SEM 0.65)

AA, arachidonic acid; CPG, cationic propyl gallate; SEM, standard error of the mean.

TABLE 68 Test characteristics (other, monotherapy)

Study	Details of kit (manufacturer)	Anticoagulant (concentration)	Agonist (concentration)	Time since last aspirin dose
Monotherapy at time of PFT and during follow-up				
Flow cytometry				
Frelinger 2009[76]	Flow cytometry (FACSCalibur™ flow cytometer, BD Biosciences, Franklin Lakes, NJ, USA)	No details	No details	No details
Monotherapy at time of PFT, dual during follow-up				
Flow cytometry				
Kaminska 2007[196]	Flow cytometry	No details	AA Collagen	Up to 24 hours
Surgicutt II				
Buchanan 2000[152]	Surgicutt II bleeding time device (ITC Commercial Group, Piscataway, NJ, USA)	No details	No details	First testing: up to 24 hours Repeat testing: when each patient had not taken aspirin for a minimum of 7 days
Apact II platelet aggregometer				
Stejskal 2006[198]	Apact II platelet aggregometer (Labitec GmbH, Ahrensburg, Germany)	No details	CPG 3 µM concentration	Up to 24 hours
Platelet reactivity test				
Grotemeyer 1993[154]	Platelet reactivity test (newly developed modification – reference cited[233])	No details	EDTA	12 hours
Impact-R® (cone and platelet analyser test)				
Monotherapy at time of PFT and during follow-up				
Schwammenthal 2008[125]	Impact-R® (cone and platelet analyser test)	No details	AA (1.6 mM)	At least 6 hours before blood sampling
Monotherapy at time of PFT, dual during follow-up				
Spectre 2011[93]	Impact-R® (cone and platelet analyser test)	Sodium citrate	AA (0.32 mM)	Up to 24 hours

AA, arachidonic acid; CPG, cationic propyl gallate; EDTA, ethylenediaminetetraacetic acid.

As it was not possible to compare directly across tests or to usefully summarise results, there has been no discussion on the quality of studies and no presentation of results. For reference, the main quality characteristics are presented in *Tables 69–72* and extracted results can be found in the webpage linked to the report (http://medweb4.bham.ac.uk/NIHR_Aspirin_Resistance/).

TABLE 69 Risk of bias, patient selection (other, monotherapy)

Domain 1: patient selection	Was a consecutive or random sample of patients enrolled?	Was patient selection independent of patient outcomes?	Were reasons for any posteligibility exclusions provided?
Monotherapy at time of PFT and during follow-up			
Flow cytometry			
Frelinger 2009[76]	Consecutive	Yes	Stated that less than 3% of eligible patients declined participation (reason not given)
Monotherapy at time of PFT, dual during follow-up			
Flow cytometry			
Kaminska 2007[196]	No details	Yes	No details
Surgicutt II			
Buchanan 2000[152]	Consecutive	Yes	15% of those recruited withdrew from the study; 28% of those who continued were excluded as a result of non-compliance
Apact II platelet aggregometer			
Stejskal 2006[198]	No details	Yes	No details
Platelet reactivity test			
Grotemeyer 1993[154]	Consecutive	Yes	No details
Impact-R® (cone and platelet analyser test)			
Monotherapy at time of PFT and during follow-up			
Schwammenthal 2008[125]	Consecutive	Yes	No details
Monotherapy at time of PFT, dual during follow-up			
Spectre 2011[93]	Consecutive	Yes	No details

TABLE 70 Risk of bias, PFT (other, monotherapy)

Domain 2: PFT	If a threshold was used, was it prespecified?	How was the threshold derived (e.g. literature cut-off, based on study data)?	Is the undertaking and interpretation of the index test blinded to the patient characteristics (including clinical outcomes)?
Monotherapy at time of PFT and during follow-up			
Flow cytometry			
Frelinger 2009[76]	No details (appears to be a threshold as OR calculated)	No details	No details
Monotherapy at time of PFT, dual during follow-up			
Flow cytometry			
Kaminska 2007[196]	Not explicitly stated; assumed that if there is any aggregation patients are classed as aspirin resistant	No details	No details
Surgicutt II			
Buchanan 2000[152]	Yes; coefficient of variation between on and off aspirin bleeding times > 26% is an aspirin responder Coefficient of variation between on and off aspirin bleeding times ≤ 26% classified as aspirin resistant	A pilot study with healthy volunteers was performed to determine the reproducibility of the Surgicutt II bleeding time test as performed by the BRAT study nurses and technicians, and to determine the biological variability of the bleeding times over 10 weeks	No details
Apact II platelet aggregometer			
Stejskal 2006[198]	Yes; a patient was considered to be an 'aspirin responder' (without aspirin resistance) if spontaneous aggregation was below 5%	No details	No details
Platelet reactivity test			
Grotemeyer 1993[154]	Yes (platelet reactivity value > 1.25)	Stated that patients arbitrarily subdivided (author's own reference cited[234])	No details
Impact-R® (cone and platelet analyser test)			
Monotherapy at time of PFT and during follow-up			
Schwammenthal 2008[125]	Yes; partial response 20–39% vs. good response < 20%	Literature cited[149]	Unclear; treating physicians and the investigators evaluating the patients were blinded to the results of the platelet function studies
Monotherapy at time of PFT, dual during follow-up			
Spectre 2011[93]	Yes, but no specific values; tertiles of percentage surface coverage of adherent platelets	Tertiles	No details

BRAT, Benefits and Risks of ASA [acetylsalicylic acid] on Thrombosis.

TABLE 71 Risk of bias, outcomes and study attrition (other, monotherapy)

Domains 3 and 4: outcomes and study attrition	Were the outcomes of interest clearly defined in advance?	Were the outcome results interpreted without knowledge of the results of the PFT?	What was the proportion of missing data? (State reasons for loss to follow-up or differences in those who completed or were lost)
Monotherapy at time of PFT and during follow-up			
Flow cytometry			
Frelinger 2009[76]	Yes	Yes; all clinical outcome data obtained by research personnel blinded to results of PFTs	127/682 lost to follow-up (for MACE outcome)
Monotherapy at time of PFT, dual during follow-up			
Flow cytometry			
Kaminska 2007[196]	No – the paper did not focus on clinical outcomes; it was focused on the results of the PFTs	Yes	The paper states that one person (out of 27) was lost to follow-up at 6 months as a result of MI; this is the same person who is recorded as having the clinical event of MI
Surgicutt II			
Buchanan 2000[152]	Yes	Yes; outcome assessors unaware of aspirin responder status	227/516 lost to follow-up at 2 years (withdrawal or exclusion because of non-compliance)
Apact II platelet aggregometer			
Stejskal 2006[198]	Yes (broadly)	No details	Appeared to be no loss to follow-up
Platelet reactivity test			
Grotemeyer 1993[154]	Yes	No details	6/180 lost to follow-up
Impact-R® (cone and platelet analyser test)			
Monotherapy at time of PFT and during follow-up			
Schwammenthal 2008[125]	Yes	Yes; treating physicians and the investigators evaluating the patients were blinded to the results of the platelet function studies	Follow-up data were available for 81/105 patients (77%)
Monotherapy at time of PFT, dual during follow-up			
Spectre 2011[93]	Yes	No details	7/63 lost to follow-up at 6 months

TABLE 72 Risk of bias, confounders (other, monotherapy)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Monotherapy at time of PFT and during follow-up						
Flow cytometry						
Frelinger 2009[76]	Design: N/A Analysis: yes (OR)	Sex, TIMI risk score, aspirin dose, platelet count, BMI, use of clopidogrel, statins and oral hypoglycaemic agents	N/A	Not specifically	By TxB_2 levels	'Two patients had serum TXB2 levels in the range observed for aspirin-free healthy controls, and their platelet function was therefore consistent with aspirin noncompliance. Because "resistance" cannot be distinguished from noncompliance, these subjects were not excluded from follow-up'
Monotherapy at time of PFT, dual during follow-up						
Flow cytometry						
Kaminska 2007[196]	Design: N/A Analysis: no	N/A	N/A	No details	No details	No details
Surgicutt II						
Buchanan 2000[152]	Design: N/A Analysis: no	N/A	N/A	Yes	A blood sample was collected at the time of each bleeding time test and processed for a platelet TxA_2 determination as a measure of patient compliance. Non-compliance resulted in the exclusion of any patient data from the study analysis	28% (148 participants) were excluded from the data analysis as a result of non-compliance

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Apact II platelet aggregometer						
Stejskal 2006[198]	Design: N/A Analysis: no	N/A	No details	No details	No details	No details
Platelet reactivity test						
Grotemeyer 1993[154]	Design: N/A Analysis: yes (HR)	Model 1: age, responder/ non-responder, risk factors present/absent, previous smoking, pre-existing vascular diseases, therapy with diuretics Model 2: responder/ non-responder, risk factors present/absent, previous smoking, pre-existing vascular diseases, therapy with diuretics Model 3: responder/ non-responder, accumulation of risk factors, previous smoking, accumulation of pre-existing vascular diseases, therapy with diuretics	No details	Yes	Patients who had stopped taking aspirin were excluded	Four patients did not comply

continued

TABLE 72 Risk of bias, confounders (other, monotherapy) (*continued*)

Domain 5: confounding	Are confounders accounted for in the design or analysis (e.g. adjustment, stratification)?	If there is an adjusted outcome measure (e.g. OR, HR), what were the factors that were adjusted for?	If a HR was presented, was the proportional hazards assumption met?	Was compliance measured?	How was compliance measured?	Level of compliance
Impact-R® (cone and platelet analyser test)						
Monotherapy at time of PFT and during follow-up						
Schwammenthal 2008[125]	Design: N/A Analysis: yes (for OR)	Age, NIHSS, diabetes	N/A	No details	No details	No details
Monotherapy at time of PFT, dual during follow-up						
Spectre 2011[93]	Design: N/A Analysis: yes (for HR)	'Variables chosen for inclusion into the model were those that tended to be associated with event-free survival on univariate analysis and age'	No details	No details	No details	No details

BMI, body mass index; N/A, not applicable; TIMI, thrombolysis in myocardial infarction.

Population and test characteristics

Seven studies[76,93,125,152,154,196,198] were identified in this category.

In two studies[76,196] the test performed was flow cytometry. In two other studies[93,125] the test performed was Impact-R® (cone and platelet analyser test). Other tests were bleeding time by Surgicutt II (one study),[152] cationic propyl gallate-induced aggregation (one study)[198] and the 'platelet reactivity test' (one study).[154]

Populations comprised patients with CVD/stroke (two studies),[125,154] CAD (one study)[76] and ACS (one study),[198] and those undergoing non-urgent CABG[152] and PPCI.[93] There was one study[196] in patients with UA/ACS undergoing PPCI. One study included only patients with a first and recent MI,[196] and no other studies reported how long patients had had their primary underlying condition for.

In four studies[125,152,154,198] it appeared that patients were exclusively on monotherapy both at the time of the PFT and during follow-up. In one study,[125] around 4% of patients were on dual therapy (+ clopidogrel) at the time of the PFT. Given the small proportion on dual therapy, these studies have been included in the 'monotherapy' category.

In a further study,[76] patients were on monotherapy at the time of the PFT, and around 32% went on to additionally receive clopidogrel at some point during follow-up. It is possible that not all studies have reported where a proportion of patients commenced additional therapies during follow-up.

In two studies[93,196] patients were on monotherapy at the time of the PFT and all were on dual therapy (+ clopidogrel) during follow-up. These studies have been listed separately, as the addition of clopidogrel therapy in all patients may affect the rate of events, and may also be a reflection of underlying population differences compared with the other studies.

Comedications across studies, where reported, included statins, COX-2 antagonists, heparin, warfarin, beta-blockers, ACE inhibitors, calcium channel blockers, diuretics, insulin, oral hypoglycaemics and antidepressants.

Non-steroidal anti-inflammatory drugs were not permitted (or had to be discontinued within a certain time period) in two studies.[196,198] One study[76] stated that 10% of patients were on NSAIDs, and there were no details on NSAIDs in the remaining studies.

The number of participants in the studies ranged from 27 to 700 (see *Table 67*). Where reported, mean ages of patients ranged from 58 to 64 years, with most means around the early 60s. There were more men than women across all studies, with proportions of men ranging from 52% to 86%. The proportion of patients with diabetes ranged from 20% to 44%, and that of smokers from 19% to 37% (where reported; see *Table 67*). All studies were conducted in hospital settings.

The dose of aspirin ranged between 75 mg/day and 500 mg/day. Details were variable across studies regarding the length of time patients had been receiving aspirin therapy, with some noting a minimum period, and some whether patients were chronic or first time users (see *Table 67*). No study stated whether aspirin was provided in enteric or plain form, though one study[93] noted that aspirin was in chewable form.

The main study characteristics were listed in *Table 67*. Note that in some studies baseline characteristics have been reported only according to resistant/sensitive groups or groups with/without diabetes, rather than for the total study population.

Studies noted that there were at least 6 hours (one study[125]) and 12 hours (one study[154]) between aspirin dose and PFT. Five other studies[93,147,152,196,198] stated that there were up to 24 hours between aspirin dose and PFT (see *Table 68*).

Studies with more than one test

Fourteen studies undertook more than one PFT (*Table 73*); however, there were very few data that could be compared given the differences in reported outcomes and outcome statistics. Thus, data from only four studies[99,108,112,162] have been presented in forest plots (*Figures 55–58*). These included the two studies that compared most PFTs.[99,162] The unadjusted OR was the most frequently reported statistic and thus provided most information.

Note that data from all studies, on all reported outcomes and reported or calculable outcome statistics, are presented in the main results sections.

TABLE 73 Studies with more than one test

Study	LTA	VerifyNow® Aspirin	PFA-100®	TxA_2	WBA	TEG	Other	Outcomes reported
Addad[108]			✓	✓				MACEs
Frelinger[76]			✓	✓			✓ (flow cytometry)	MACEs, death
Gluckman[99]		✓	✓	✓	✓			Ischaemic/thrombotic events
Kaminska[196]					✓		✓ (flow cytometry)	Death, ischaemic/ thrombotic events
Linnemann[112]	✓		✓					MACEs, ischaemic/ thrombotic events
Lordkipanidzé[162]	✓	✓	✓	✓	✓			MACEs
Majeed[117]					✓	✓		Ischaemic/thrombotic events
Miyata[164]	✓			✓				MACEs
Modica[187]	✓ (PA-200)		✓					MACEs
Payne[147]	✓						✓ (flow cytometry)	Death, ischaemic/ thrombotic events
Schwammenthal[125]	✓						✓ (Impact-R®)	Ischaemic/thrombotic events
Sobol[186]			✓		✓			Death
Spectre[93]	✓						✓ (Impact-R®)	MACEs
Tan[174] (abstract)	✓					✓		Death, ischaemic/ thrombotic events

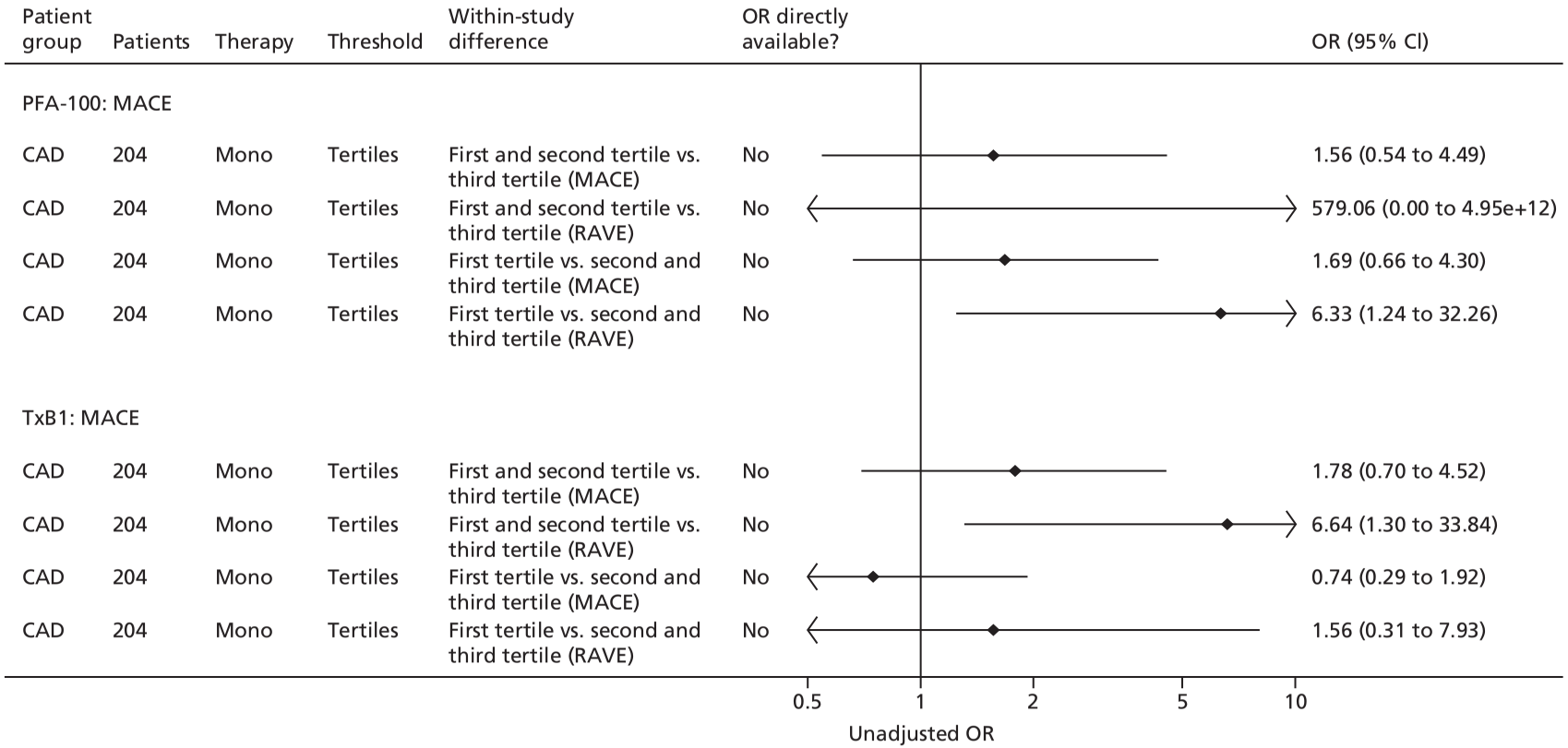

FIGURE 55 Study comparing PFA-100® and thromboxane metabolite measurement (Addad[108]). RAVE, recurrent acute vascular event.

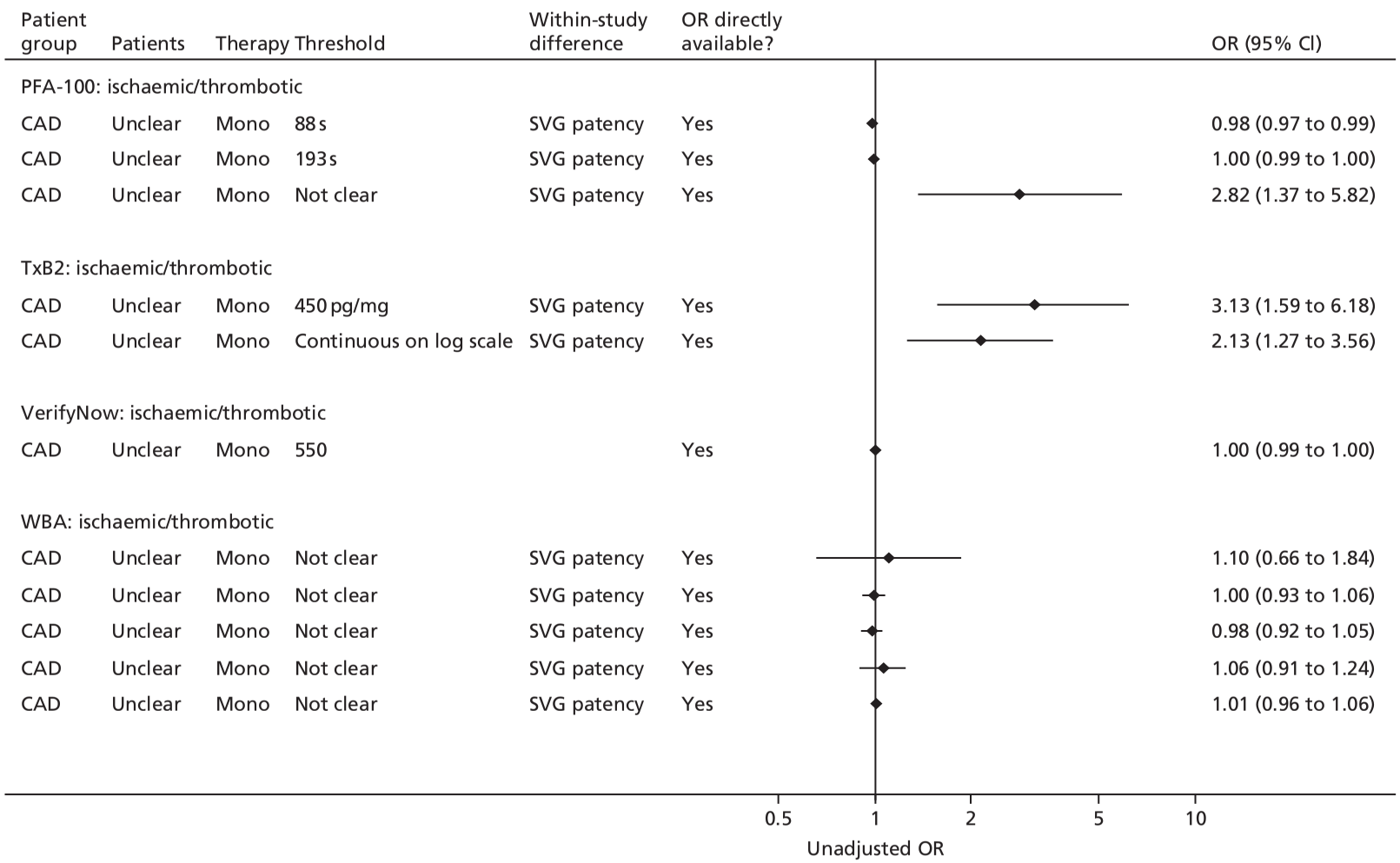

FIGURE 56 Study comparing PFA-100®, thromboxane metabolite measurement, VerifyNow® Aspirin and WBA (Gluckman[99]). s, seconds.

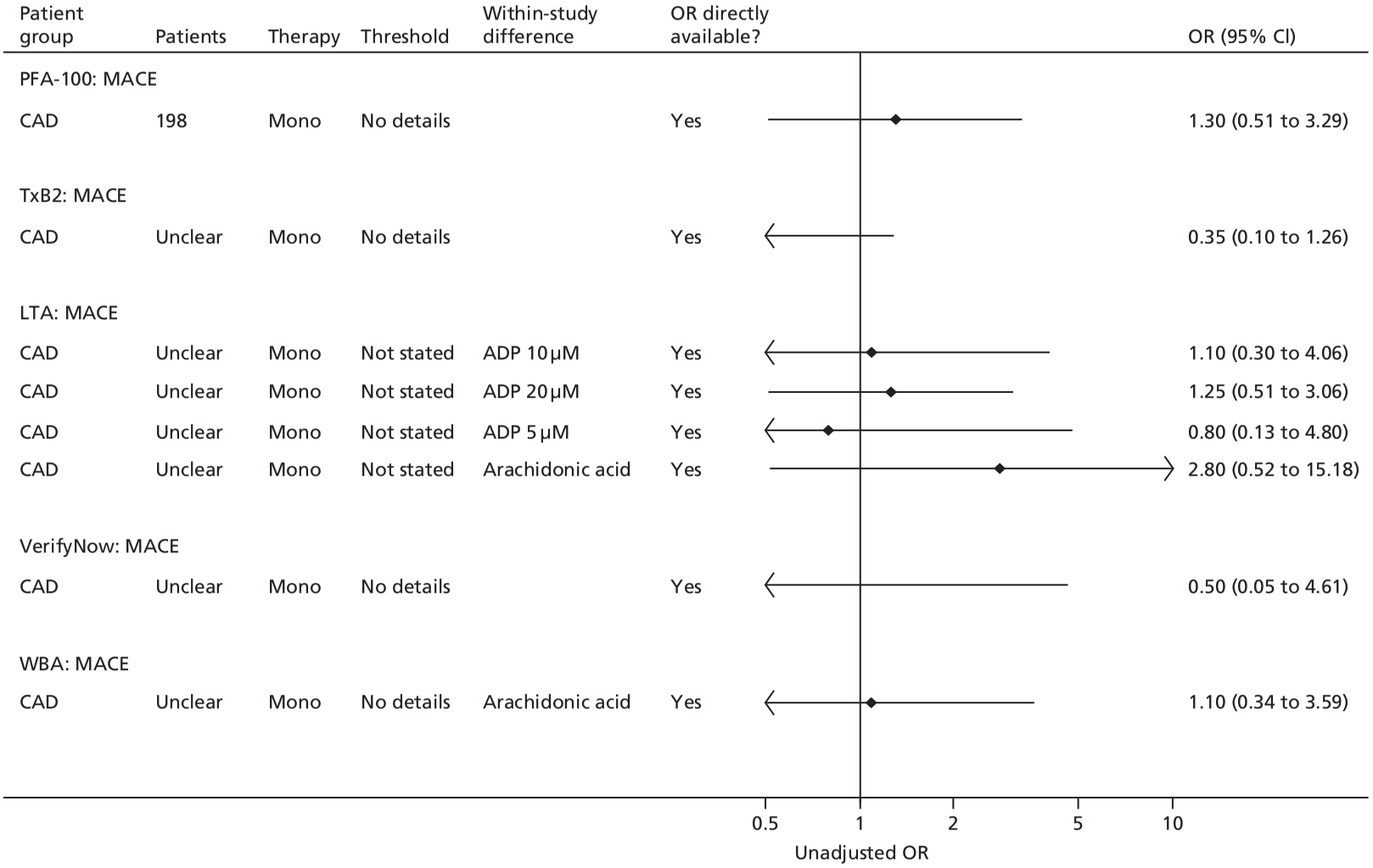

FIGURE 57 Study comparing PFA-100®, thromboxane metabolite measurement, LTA and WBA (Lordkipanidzé[162]).

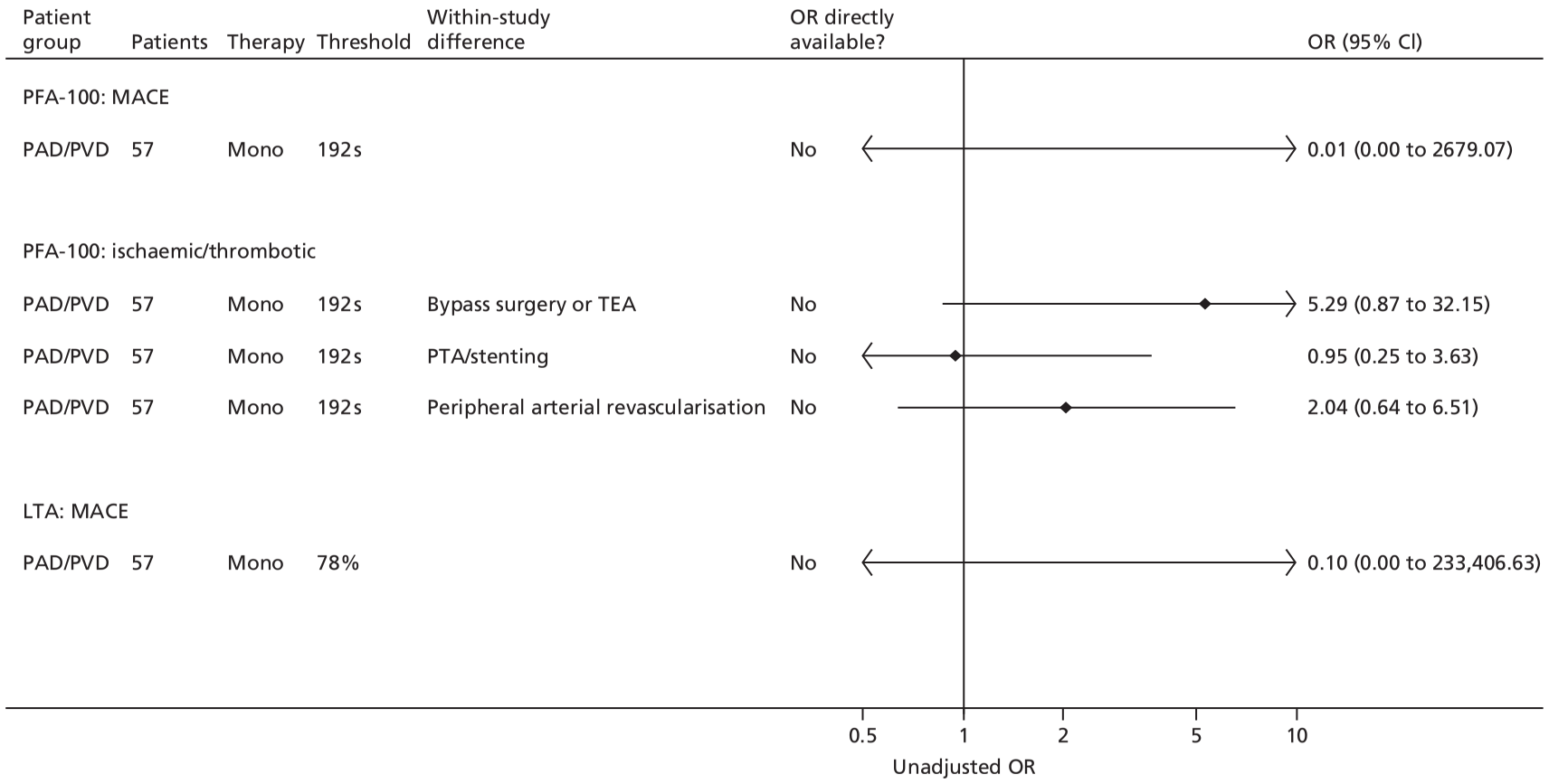

FIGURE 58 Study comparing PFA-100® and LTA (Linnemann[112]). PTA, percutaneous transluminal angioplasty; s, seconds; TEA, thoracic epidural analgesia.

Within-study comparisons

The study by Addad *et al.*[108] used two tests, PFA-100® and thromboxane; there is a lack of consistency both within and between the different tests in terms of direction of effect and statistical significance. For example, when comparing the first tertile with the second and third (as a threshold) tertiles, there are more events in the resistant group with PFA-100®, and more events in the sensitive group with a thromboxane test. Gluckman *et al.*[99] compared four tests; again there is no consistency across tests in terms of how many individuals are classified as resistant or sensitive. Patients classified as resistant by a thromboxane PFT are, for example, more likely to have an event (compared with the sensitive group) than those classified as resistant by WBA, where there is no difference in event rate between resistant and sensitive. This lack of consistency in direction of effect is further demonstrated by the studies by Lorkipanidzé *et al.*[162] and Linnemann *et al.*[112] Clearly, the choice of test and threshold will influence whether an individual is classified as resistant or sensitive.

Between-study comparisons

Given the inconsistency within studies, the added heterogeneity between studies and the limited number of data, a comparison across studies of the direction of effect for individual PFTs is not feasible.

Dual therapy

The tests identified for assessing platelet function in patients on dual therapy (aspirin plus a second antiplatelet agent) are (i) LTA induced by arachidonic acid, (ii) VerifyNow® Aspirin, (iii) measurement of urinary or serum/plasma 11-dehydro-TxB_2 concentrations, (iv) PFA-100®, (v) WBA induced by arachidonic acid, (vi) TEG and (vii) other miscellaneous tests. *Table 3* identified the studies that have used these tests in a dual-therapy population.

The original intention was to report and analyse these studies in a similar way to the studies in patients receiving monotherapy with aspirin. However, the finding of limited evidence of the prognostic utility of platelet function testing related to aspirin monotherapy led to the decision not to undertake such analyses in dual-therapy studies.

Data on the population and test characteristics, along with quality characteristics of the studies in patients undergoing platelet function testing while receiving dual therapy, were, however, extracted and are included in the data extraction database (see *Appendix 4*). Should the need for these studies to be analysed exist in the future, this work can build on the data already collected.

Studies in patients with diabetes

No studies in a solely diabetic population were included in this review.

Prognostic models

The methods of this systematic review allowed for the inclusion of available prognostic models in which a PFT is one of multiple prognostic factors predicting clinical outcomes in a population of interest.

No such models were identified.

Systematic reviews

Fifteen systematic reviews were identified that met the initial inclusion criteria (*Table 74*).[203–217] On more detailed scrutiny, two reviews did not link the results of PFTs to clinical outcomes (one review on pharmacogenetics[203] and one on the role of PFTs in guiding clinical practice which did not provide prospective follow-up of clinical outcomes[204]). A further review[205] was predominantly focused on patients with renal insufficiency and therefore is not discussed further.

The remaining 12 reviews all included relevant populations and at least some primary studies where the results of a PFT were linked to clinical outcomes.

One review was in abstract form only;[206] the authors were contacted for further details but no response was obtained.

Most reviews did not restrict inclusion of studies by type of PFT, except two,[207,208] both of which focused on the PFA-100® test only.

Only four reviews specified whether studies with patients receiving monotherapy or dual therapy were included, three including both monotherapy and dual therapy studies[206,209,210] and one stipulating monotherapy only.[207]

Few reviews provided details on whether only prospective or also retrospective studies were included (four studies provided this information[208–211]), but it appears that many included both, in some cases separating them in analysis.

All the reviews reported details of at least one database search (as per the inclusion criterion for this report). However, most presented only limited additional details on methodological aspects. Searches were limited to PubMed or MEDLINE and citation checking in half the reviews.[206,207,210,212–214] Five reviews supplied no further methodological details beyond the basic search strategy,[206,210,212–214] with a further three reporting limited details on study inclusion or exclusion criteria.[207,215,216] Four reviews reported more comprehensive methodological details[208,209,211,217] and these papers were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist.

The reviews included between 5 and 84 studies (not restricted by PFT), or between 5 and 31 studies where restriction to monotherapy studies was made clear. The review with the highest number of included studies, both overall and monotherapy, was Velkovic and Coulthard[206] a conference abstract with no listing of citations. By PFT, the highest number of studies identified by any review was 15 PFA-100® studies.[208,216] By comparison, the current review found 57 distinct monotherapy studies overall[46,76,86,88,90,92,93,95,99,105,108–110,112,113,115–118,121,123,125,127,128,132,133,135,137,138,142,144–155,159,162–164,166,168,169,171,174,186,187,189,193,195,196,198,201,202] (and 21 monotherapy studies using the PFA-100® test[76,99,108,109,112,115,116,118,123,127,132,135,137,138,144,145,150,162,186,187,189,193]), despite using more stringent inclusion criteria including a restriction to prospective studies only. Including mono-, dual- and triple-therapy studies, 21 of the studies identified in this review[46,127,132,134,135,137–143,145,148–154,198] were also included in the seven previous reviews[207–209,211,215–217] which provided any information on exclusion criteria (see *Table 75*). Conversely, of the studies included by at least one other review, the current review excluded 16 at the full-text stage[38,235–249] and seven at the title and abstract stage,[250–256] as they did not meet the inclusion criteria. Three studies were included in other reviews which were not identified by the search strategy; one was subsequently excluded as it was a cross-sectional study,[256] while the correct citation was not identifiable for the other two studies.[219,257]

TABLE 74 Systematic reviews identified

Review	Searches up to	Research question	Systematic review methodology	Number of included studies	Population	Monotherapy only or monotherapy and dual therapy included	PFTs	Prospective follow-up of clinical outcomes	Aspirin resistance/ sensitivity linked to clinical outcomes?
Included systematic reviews									
Musallam 2011[212]	No details	Mechanisms, laboratory evaluation, clinical impact and management of resistance to aspirin and clopidogrel therapy	MEDLINE and PubMed search; no language/ publication year restrictions; citation checking. No further methodological details	Reviews by Krasopoulos (2008)[209] and Snoep (2007)[217] discussed, also nine studies described individually	Patients with cardiovascular disease	Not specified	Not specified	Yes	Yes
Cañivano Petreñas 2010[215] (Spanish)	November 2008	Prevalence, epidemiology, mechanism of action and clinical consequences of aspirin resistance	PubMed, EMBASE and other databases searched up to 2008. Citation checking. Some details on selection criteria. No further methodological details	16 studies linking aspirin with clinical outcomes	Patients at high risk of cardiovascular events	Not specified	Any PFT as long as methods defined	Yes	Yes
Velkovic 2009[206] (conference abstract)	No details	Platelet function test options, and the epidemiology, aetiology and management of antiplatelet agent low response	PubMed search described as 'systematic'. No further methodological details	31 aspirin and 53 dual-therapy studies included, but citations not listed	Patients undergoing endovascular procedures	Aspirin, clopidogrel or both	Not specified	Unclear, but longer term outcomes are mentioned	Yes

continued

TABLE 74 Systematic reviews identified (*continued*)

Review	Searches up to	Research question	Systematic review methodology	Number of included studies	Population	Monotherapy only or monotherapy and dual therapy included	PFTs	Prospective follow-up of clinical outcomes	Aspirin resistance/ sensitivity linked to clinical outcomes?
Crescente 2008[207]	October 2007	Prevalence of non-responders to aspirin, and clinical and methodological factors that can influence it and its possible association with vascular outcomes	Details of search strategy in PubMed only, citation checking. Exclusion criteria listed. No further methodological details	Eight studies linking aspirin with clinical outcomes	Patients taking aspirin for primary or secondary prevention of vascular events	Monotherapy only	PFA-100® only	Yes	Yes
Ferguson 2008[210]	November 2007	Variability of antiplatelet resistance, factors associated with resistance, causes and approaches to overcoming resistance	Search strategy for PubMed only. No further methodological details	States that only prospective, controlled trials included; 17 trials identified (appears to include prospective cohorts) Results from four and seven studies respectively described as linking clinical outcomes to aspirin and clopidogrel resistance	Patients with CAD	Aspirin and/or clopidogrel	Not specified	Yes	Yes
Pusch 2008[216]	March 2008	Prevalence of aspirin resistance and its association with clinical outcome; treatment approaches	Search strategy for MEDLINE, PubMed and The Cochrane Library, citation checking. Some detail on selection criteria. No further methodological details	LTA: 11 studies TxB_2: 5 studies PFA-100®: 15 studies WBA and Ultegra RPFA-ASA system: 4 studies Total of 35 studies	Patients taking aspirin for primary or secondary prevention of vascular events	Not specified	Not specified	Yes	Yes

Review	Searches up to	Research question	Systematic review methodology	Number of included studies	Population	Monotherapy only or monotherapy and dual therapy included	PFTs	Prospective follow-up of clinical outcomes	Aspirin resistance/ sensitivity linked to clinical outcomes?
Reny 2008[208]	July 2007	Clinical predictive value of PFA-100® in aspirin-treated cardiovascular patients	Details of search strategy, study selection, data extraction and methods of analysis (see *Critical appraisals* for further details)	15 studies (eight prospective and seven non-prospective)	Patients with symptomatic atherosclerosis	Not specified	PFA-100® only	Yes	Yes
Sofi 2008[211]	May 2007	Residual platelet reactivity in coronary heart disease patients in relation to the occurrence of adverse coronary events during follow-up	Details of search strategy, study selection, data extraction and methods of analysis (see full quality appraisal for further details)	11 prospective studies	Patients with coronary heart disease	Not specified	Not specified	Yes	Yes
Krasopoulos 2008[209]	Unclear ('to present')	Relationship between aspirin resistance and clinical outcomes in patients with cardiovascular disease	Details of search strategy, study selection, quality assessment and methods of analysis (see full quality appraisal for further details)	20 studies described as prospective included	Patients prescribed aspirin as antithrombotic therapy	Mono or dual	Not specified	Yes	Yes

continued

TABLE 74 Systematic reviews identified (*continued*)

Review	Searches up to	Research question	Systematic review methodology	Number of included studies	Population	Monotherapy only or monotherapy and dual therapy included	PFTs	Prospective follow-up of clinical outcomes	Aspirin resistance/ sensitivity linked to clinical outcomes?
Snoep 2007[217]	October 2006	Relationship of laboratory aspirin resistance to risk of cardiovascular recurrent events	Details of search strategy, study selection, quality assessment and methods of analysis (see full quality appraisal for further details)	15 full-text articles and one abstract	Patients with established CAD, CVD or PAD	Not specified	Not specified	Yes	Yes
Wong 2004[213]	January 2003	Evidence for aspirin resistance in patients with atherosclerosis (mechanism, prevalence, definition, clinical outcomes)	Details of search strategy (MEDLINE) only; citation checking. No further methodological details. Mainly narrative approach	Five studies described narratively in terms of resistance and clinical outcomes	Patients with atherosclerosis	Not specified	Not specified	Yes	Yes
Howard 2002[214]	February 2002	Significance of aspirin resistance in vascular patients	Details of search strategy (MEDLINE) only up to 2002; citation checking. No further methodological details. Mainly narrative approach	Five studies described narratively in terms of resistance and clinical outcomes	Not prespecified. Patients with cardiovascular disease, CVD and PVD	Not specified	Not specified	Yes	Yes

Review	Searches up to	Research question	Systematic review methodology	Number of included studies	Population	Monotherapy only or monotherapy and dual therapy included	PFTs	Prospective follow-up of clinical outcomes	Aspirin resistance/ sensitivity linked to clinical outcomes?
Less relevant reviews in the current context									
Verschuren 2012[203]	May 2011	Pharmacogenetics: genetic markers linked to platelet activity or clinical outcomes	Details of search strategy in MEDLINE only (included citation checking). Few details on selection criteria. No further methodological details	None specifically looking at resistance and clinical outcomes	Patients with cardiovascular disease	Not specified	Not specified	Yes	No
El-Menyar 2010[205]	February 2009	Risk of stent thrombosis in patients with renal insufficiency	MEDLINE, Scopus and EBSCO*host* searched. Limited details on search strategy, but no other methodological details	One study only cited for dual antiplatelet non-responsiveness in this population	All patients with chronic renal insufficiency after PCI	Not specified	Not specified	Yes	Yes
Dickinson 2008[204]	No details	Role of PFTs in guiding surgical practice	Search strategy for MEDLINE and PubMed only. No further methodological details	Three studies referred to narratively	Patients undergoing surgery	Not specified	TEG, VerifyNow® Aspirin, PFA-100®, ACT, Sonoclot® (Sienco®, Arvada, CO), CSA in search terms	No	No

ACT, activated clotting time; CSA, Clot Signature Analyzer.

Critical appraisals

Four reviews[208,209,211,217] reporting more comprehensive methodological details were critically appraised using the AMSTAR checklist. Significant information was nevertheless found to be lacking from all four publications which would enable a complete assessment of the validity of their conclusions.

Krasopoulos *et al.*'s[209] review focused on the relationship between aspirin resistance and clinical outcomes in patients with cardiovascular disease, and identified 20 studies totalling 2930 patients. The paper provided no details of a protocol or whether or not the research question and inclusion criteria were prespecified. As no search strategy was presented, it was difficult to gauge whether or not the strategy was likely to have included all potentially relevant studies; thus, it was not possible to determine whether the reduction from the 36,573 articles identified by the initial search to 320, using only the term 'aspirin resistance', was appropriate or had resulted in the omission of relevant studies. It appeared that only a small proportion of identified articles (57/320) were reviewed independently, but that each of the authors reviewed and tabulated data from every included paper. Four bibliographic databases were searched, and citations (from 210 papers) were reviewed. Nevertheless, there was no mention of searching grey/unpublished literature (including ongoing trials or conference abstracts) or contacting experts. Although a list of included studies was provided, one was not provided for the excluded studies.

Although the authors presented the characteristics of included studies, there were no details on thresholds (for determining resistance) or on follow-up time, and limited information on the use of a prospective or retrospective study design, all of which may have influenced the event rate in the two groups. A further concern is that though the method of establishing compliance was considered, the authors considered that aspirin status measured in hospital could be assured independent of non-compliance, and further stated that it is unlikely that patients would subsequently become non-compliant, which seems an unwarranted assumption when there might be a long follow-up period. Furthermore, as it appeared that both prospective and retrospective studies had been included in the review, compliance with treatment in hospital may not reflect previous compliance with treatment.

The authors assessed included studies using a quality rating, but it was unclear how this was derived and which specific criteria were considered, and therefore it was not possible to make a judgement on the robustness of the quality assessment, or whether their assessment was correct that the few studies (3/20) rated as not having a low risk of bias were insignificant in affecting overall results. A high level of heterogeneity was evident but a fixed-effects model was used incorrectly. Given the high level of heterogeneity (potentially due to study design, study quality, underlying disease, follow-up time, type of PFT, threshold and level of compliance), the exploration of heterogeneity was limited. This, coupled with a failure to differentiate adjusted and non-adjusted results, reduced confidence in the reported conclusion that aspirin-resistant patients are at greater risk of long-term cardiovascular morbidity [OR of any cardiovascular event 3.85, 95% CI 3.08 to 4.80; $p < 0.001$ overall, or OR 3.53, 95% CI 2.66 to 4.68; $p < 0.001$ in monotherapy (14 studies)].

The review by Reny *et al.*[208] considered the clinical predictive value of only one PFT, PFA-100®, in aspirin-treated cardiovascular patients, and found seven non-prospective and eight prospective studies, incorporating 1466 and 1227 patients respectively. Again, no details were provided about the existence of a protocol or whether or not the research question was prespecified, though inclusion criteria were clearly stated. Three databases were searched, and reference lists of studies and conference abstracts were also examined. However, only English-language studies were searched for. Study selection and data extraction were conducted independently by two reviewers, and disagreements were resolved by discussion among all authors. Lists of included studies and studies excluded at full-text stage, were provided.

The authors' assessment of study quality was extremely limited. Whether or not assessment was blinded for biologists and clinicians was considered (though ill-defined), and results were found to be similar in studies whose reports explicitly mentioned blinding compared with those that did not mention the use of blinded assessments. However, the issue of blinded assessment appeared to be the only mention of study

quality considered consistently. The discussion considered some other methodological limitations of the included studies, for example lack of assessment of patient compliance (on which no data were provided by individual study), sample size and non-evaluation of von Willebrand factor. However, it was apparent that none of these assessments of methodological rigour and scientific quality were specified a priori.

Prospective and non-prospective studies were considered separately. However, adjusted and non-adjusted results were not distinguished. The heterogeneity of the prospective studies was assessed, and found to be non-significant using a random-effects model. The difference in thresholds used in the studies was recognised and discussed. Perhaps as a result of the small number of (prospective) studies, subgroup analysis was restricted to narrative discussion, and then focused on the prevalence of non-responders as opposed to the relationship with cardiovascular events. A more detailed exploration of heterogeneity was lacking and would have been desirable in interpreting the review's findings. Publication bias was considered with regard to non-prospective studies, but the funnel plot for prospective studies was not discussed.

The authors concluded that high residual platelet reactivity (i.e. non-responder status) in cardiovascular patients treated with aspirin was associated with recurrent ischaemic events. In the prospective studies they included the OR for the recurrence of an ischaemic event in aspirin non-responders relative to aspirin responders, which was 2.1 (95% CI 1.4 to 3.4, $p < 0.001$). Although the authors acknowledged the potential impact of dosage and threshold on this association, other important caveats should be noted in light of the limited information concerning study quality in the papers incorporated in this review. Finally, it was unclear if patients in any of the studies were on aspirin alone or on dual or triple therapy.

Snoep *et al.*[217] found 16 studies in their review of the relationship between laboratory aspirin resistance and the risk of cardiovascular recurrent events. In a comprehensive, as well as a priori, search strategy, four bibliographic databases were searched, with no language restrictions, and reference lists were searched and authors contacted. However, although the search terms were listed as available from the authors, they were not presented, and there was no sample search strategy, so it was difficult to assess the appropriateness of the search strategy. Although meeting abstracts were included, there were no details regarding ongoing trials or other sources of unpublished studies. Selection, quality assessment and data extraction of studies were all independently performed by two reviewers, with disagreements resolved by consensus and discussion with a third party. A list of included, but not of excluded, studies was provided. The authors stated that a funnel plot did not suggest the existence of publication bias, but did not present it in the publication.

The authors stated that the following quality criteria were assessed: control for confounders, measurement of exposure, completeness of follow-up and blinding, and, for case–control studies, matching and case definition. There was no formal scoring system. Overall findings on the quality of all included studies were not presented. Some quality findings were reported in the discussion section, but it was uncertain if this was extensive enough to capture any potential implications of quality for the results. Furthermore, while it was stated that studies were excluded because of insufficient quality during study selection, there were no details on a quality threshold. The only reference to compliance was to note that patient adherence to treatment was assessed in only three of the studies.

The review found that 15 of the 16 included studies revealed an adverse association between laboratory aspirin resistance and occurrence of cardiovascular events, with a pooled OR across all cardiovascular outcomes of 3.8 (95% CI 2.3 to 6.1). A random-effects model was used, which is appropriate as there was evidence of heterogeneity. There was no discussion of any attempt to discriminate between adjusted and non-adjusted studies. There was some subgroup analysis by type of outcome. Given the high level of heterogeneity (potentially owing to study design, study quality, underlying disease, follow-up time, type of test, threshold and level of compliance), a more detailed exploration of heterogeneity would have been appropriate. Again, a further concern was that it was unclear if patients in any of the studies were on dual or triple therapy as opposed to aspirin monotherapy.

Sofi *et al.*[211] conducted a meta-analysis on the relationship between residual platelet reactivity in coronary heart disease patients and the occurrence of adverse coronary events, and found 11 prospective studies comprising 1952 patients. Though the aim of the study was clearly stated, as were the inclusion criteria, again there was no reference to a protocol or to a priori published research objectives. Data were independently extracted by two reviewers, and disagreements were resolved by discussion with a third investigator. However, whether or not two reviewers also independently selected studies for inclusion was unclear. Four bibliographic databases and citations from relevant original studies and review articles were searched. No detail on whether or not grey literature was searched was provided. Only included studies, and not excluded studies, were listed. Publication bias was assessed using a funnel plot of effect size against standard error. The authors report that the funnel plot was broadly symmetrical, and so consistent with the conclusion that there was no publication bias; however, the plot was not presented in the publication.

No assessment of study quality was provided. The authors did consider the heterogeneity of the included studies in the discussion, and noted that most of the studies did not systematically assess adherence to aspirin therapy or adjust for confounding factors in the multivariate statistical models (6 out of the 11 included studies reported statistical data not adjusted for potential confounders).

The authors documented a significantly increased relative risk of adverse clinical events for patients with residual platelet reactivity on aspirin treatment (relative risk 3.11, 95% CI 1.88 to 5.15; $p < 0.0001$). A random-effects model was used, appropriately, as there was significant heterogeneity (I^2 reported). Subgroup analyses were performed according to relevant specific variables (duration of follow-up, aspirin dosage, PFT and patient characteristics), and in each case the risk of clinical recurrences increased. In addition, the association remained statistically significant even after the exclusion of studies that reported only crude unadjusted data (relative risk 3.19, 95% CI 1.97 to 5.19; $p < 0.00001$). Even so, a major caveat for this review related to the lack of data on study quality, and the fact that it was unclear if patients in any of the studies were on dual or triple therapy.

All four reviews found a positive association between aspirin non-responder status and likelihood of adverse cardiovascular outcomes, despite their differences in precise research question, range of included studies (*Table 75*) and primary outcome measures. However, although the four critically appraised reviews were those with the most detailed methodological information from the relevant reviews identified, all had important deficiencies, variously:

- a lack of a rigorous and transparent approach to quality assessment
- insufficient comprehensiveness and a failure to account for the complexity of the field by not considering the effect of different PFTs, thresholds, etc.
- not distinguishing between adjusted and non-adjusted statistical data
- uncertainty regarding whether patients were on aspirin monotherapy or if those on dual therapy were merged in the analysis
- uncertainty over whether included studies were prospective or retrospective in design
- failure to account for the effect of non-compliance.

In this context, caution must be exercised in interpreting the findings from these previous reviews.

TABLE 75 Overlap between included studies in the systematic reviews

Study	Cañivano Petreñas 2010[215]	Crescente 2008[207] (PFA-100® only)	Pusch 2008[216]	Krasopoulos 2008[209]	Reny 2008[208] (PFA-100® only)	Sofi 2008[211]	Snoep 2007[217]	Current review
Andersen 2002[244]	✓	✓	✓	✓	✓	✓	✓	Excluded at full-text stage
Atiemo 2008[245]		✓	✓		✓			Excluded at full-text stage
Berroushot 2006[246]	✓		✓	✓				Excluded at full-text stage
Borna 2005[225]			✓	✓				Excluded at title and abstract stage
Bruno 2004[148]			✓					✓
Buch 2007[134]			✓					✓
Buchanan 2000[152]	✓		✓	✓			✓	✓
Chen 2004[242]	✓		✓	✓			✓	Excluded at full-text stage
Chen 2005[243]	✓			✓				Excluded at full-text stage
Cheng 2005[255]							✓	Excluded at title and abstract stage
Christiaens 2008[127]	✓							✓
Cornelissen 2006[254]			✓					Excluded at title and abstract stage
Cotter 2004[46]			✓	✓			✓	✓
Cuisset 2006[143]						✓		✓
Eikelboom 2002[151]	✓		✓				✓	✓
Faraday 2004[241]			✓	✓				Excluded at full-text stage
Fuchs 2006[138]						✓		✓

continued

TABLE 75 Overlap between included studies in the systematic reviews (*continued*)

Study	Cañivano Petreñas 2010[215]	Crescente 2008[207] (PFA-100® only)	Pusch 2008[216]	Krasopoulos 2008[209]	Reny 2008[208] (PFA-100® only)	Sofi 2008[211]	Snoep 2007[217]	Current review
Geisler 2008[256]			✓					Not identified in current search. Hard copy retrieved and excluded
Gianetti 2006[141]					✓	✓		✓
Grotemeyer 1993[154]	✓		✓	✓			✓	✓
Grundmann 2003[248]	✓	✓	✓	✓	✓		✓	Excluded at full-text stage
Gulmez 2007[253]			✓					Excluded at title and abstract stage
Gum 2001[219]		✓						Does not appear to refer to relevant citation
Gum 2003[149]	✓		✓	✓	✓	✓	✓	✓
Gurbel 2003[257]				✓				Does not appear to refer to relevant citation
Hobikoglu 2007[135]			✓		✓			✓
Hobikoglu 2005[240]		✓	✓	✓	✓			Excluded at full-text stage
Lev 2006[239]			✓				✓	Excluded at full-text stage
Linden 2007[252]					✓			Excluded at title and abstract stage
Malek 2007[238]			✓		✓	✓		Excluded at full-text stage
Marcucci 2006[139]			✓		✓	✓		✓
McCabe 2005[249]				✓				Excluded at full-text stage
Mueller 1997[153]	✓		✓	✓			✓	✓
Ohmori 2006[142]			✓					✓

Study	Cañivano Petreñas 2010[215]	Crescente 2008[207] (PFA-100® only)	Pusch 2008[216]	Krasopoulos 2008[209]	Reny 2008[208] (PFA-100® only)	Sofi 2008[211]	Snoep 2007[217]	Current review
Pamukcu 2005[251]			✓		✓			Excluded at title and abstract stage
Pamukcu 2006[140]	✓		✓		✓	✓	✓	✓
Pamukcu 2007[137]	✓		✓	✓	✓	✓		✓
Poston 2006[247]	✓		✓	✓			✓	Excluded at full-text stage
Poulsen 2007[132]			✓		✓	✓		✓
Poulsen 2007[132]			✓					Excluded at title and abstract stage
Sambola 2004[145]		✓						✓
Stejskal 2006[198]	✓		✓	✓		✓	✓	✓
Tantry 2005[38]			✓					Excluded at full-text stage
Valles 2007[237]			✓					Excluded at full-text stage
Yilmaz 2005[236]	✓	✓	✓	✓	✓		✓	Excluded at full-text stage
Zhang 2005[235]			✓	✓				Excluded at full-text stage
Ziegler 2002[150]		✓					✓	✓

Ongoing studies

The searches of research registers identified 65 potentially relevant records of apparent ongoing studies (see *Chapter 4*, *Searches* for the sources searched and *Quantity of research available*, earlier in this chapter, for the identification of these records). Copies of these records were obtained and the review selection criteria (see *Chapter 4*, *Study selection*) were applied, except for the criterion for publication type, which was ignored because it was irrelevant. Key difficulties with this selection process were the absences of information in the records given that these were not protocols for studies but only brief outlines of study aims with limited associated methodological information provided. Furthermore, it was frequently unclear whether the same record was in more than one register or some of the studies in older records had actually been completed and published.

Despite these difficulties, it was possible to identify a number of records that met the selection criteria[258–262] and also records that potentially relate to fully published articles.[263,264]

However, for the reasons mentioned, the selection process could not provide definitive sets of included and excluded records in regard to ongoing studies, and as such no lists are given in this report.

Therefore, this section only serves to indicate that there are a number of ongoing studies which may add further data in the future.

Relevant studies identified after the search cut-off dates

After the searches were undertaken for this review, further relevant studies continued to be published.[265–267] Although the authors of this report were aware of these publications, these have not been included in the above analysis to prevent the introduction of bias. A robust approach would be to update all the searches; however, given the magnitude and complexity of this project, this was beyond the resources available. An alternative approach would be to discuss the sensitivity of the review findings to the more recent subjectively identified evidence. However, given the heterogeneity of included studies, even within subgroups, and the absence of the ability to undertake any pooled analyses, this approach was considered to be of limited benefit.

Chapter 6 Economic analysis

This section has two aims: (i) to review systematically the published evidence relating to the cost-effectiveness of platelet function testing in patients on aspirin therapy with established cardiovascular disease, CVD or diabetes; and (ii) to assess the cost-effectiveness of platelet function testing plus change in treatment for patients with established CAD on aspirin therapy compared with no testing and no change in treatment, from a NHS and Personal Social Services (PSS) perspective. For this aim, a speculative economic model was developed.

The methods and findings of the systematic review are presented first followed by those of the speculative economic model.

Systematic review of cost-effectiveness studies

Methods

The broad methods of this systematic review were similar to those presented in *Chapter 4*, and thus only key details are given here.

Search strategy

Searches for economic studies were run on MEDLINE, EMBASE and NHS EED using, where appropriate, relevant terms for economic studies along with terms for clinical populations and PFTs. Examples of these strategies can be found in *Appendix 2*. The yield of articles from these searches was supplemented with any further economic evaluations and cost studies identified during screening of the search yield in the prognostic/diagnostic utility review.

Study selection

Two reviewers independently screened titles and abstracts for relevance. All potentially relevant articles were obtained for scrutiny against the full selection criteria, with any disagreements resolved by discussion. The criteria were:

- *Study design* Cost–consequence analysis, cost-effectiveness analysis, cost–benefit analysis, cost–utility analysis, cost studies.
- *Population* Patients aged ≥ 18 years on aspirin (as monotherapy or in combination with other antiplatelet agents), with established cardiovascular disease, CVD or diabetes. Studies with mixed populations were included as long as data for relevant patients were extractable.
- *Intervention* Aspirin-specific platelet function assay or global PFT where patients are receiving aspirin as the only antiplatelet therapy. The list of eligible assays has been outlined previously in *Table 2*.
- *Comparator* No assessment of aspirin resistance or current practice.
- *Outcome* Cost-effectiveness, cost estimates, utilisation estimates, quality-of-life estimates.

Data extraction and quality assessment strategy

Data on the following, where available, were extracted from included studies by one health economics reviewer and checked by another:

- study characteristics, such as study question, form of economic analysis, population, interventions, comparators, perspective, time horizon and form of modelling used
- clinical effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting and key assumptions
- results and sensitivity analyses.

Studies were quality assessed using tools as part of the data extraction process, namely the Consensus on Health Economic Criteria list[268] for economic evaluations and the checklist by Philips *et al.*[269] for model-based analyses.

Results

A total of 387 records were identified from the searches and, following the removal of duplicates, there were 299 unique records. No additional articles were identified from the process of the systematic review of prognostic/diagnostic utility studies.

None of the records was deemed relevant to this economic review and, as such, no hard copies were obtained for scrutiny against the inclusion criteria for the review.

A flow diagram presenting the process of selecting studies can be found in *Figure 59*.

Discussion

No economic evaluations or cost studies were found during the search for literature on the cost and cost-effectiveness of platelet function testing in patients with established cardiovascular disease or CVD. This is surprising given the amount of research identified by the systematic review of prognostic/diagnostic utility (see *Chapter 4*) and the degree of debate around this topic.

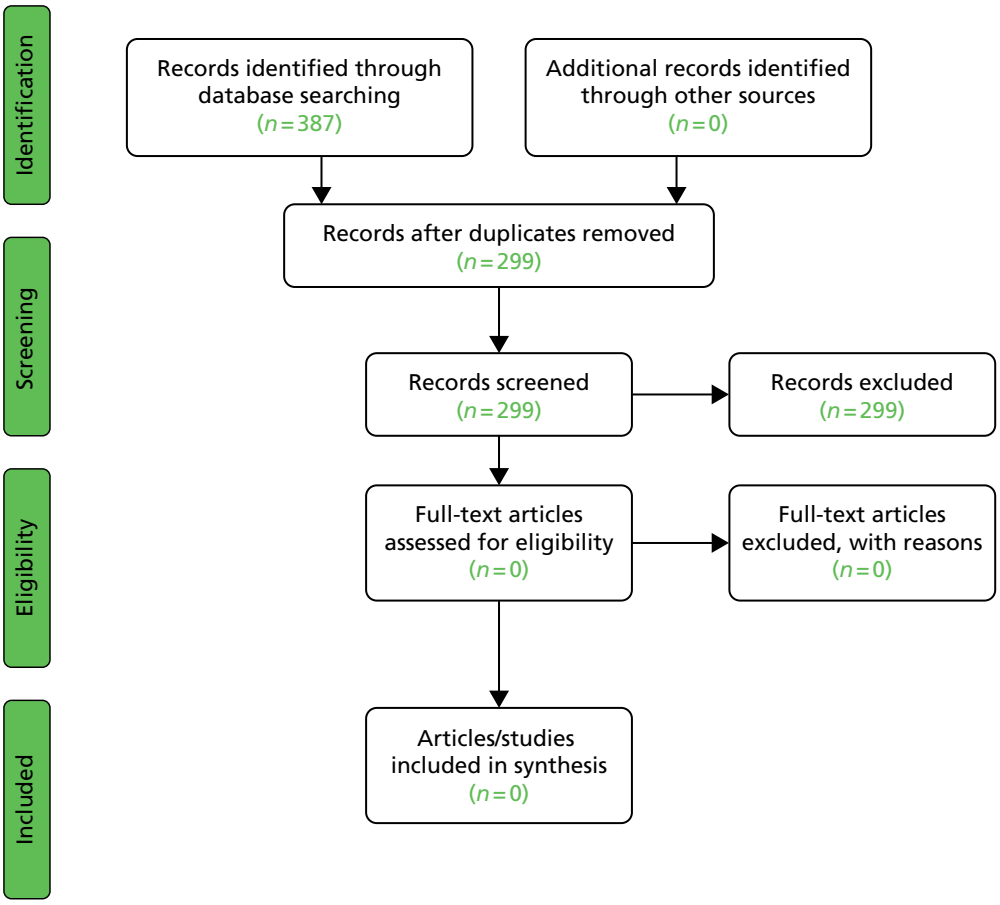

FIGURE 59 Flow diagram showing study selection for the economic evaluations review.

Economic modelling

This section provides a detailed description of the speculative economic model developed to estimate the cost-effectiveness of platelet function testing with the option of a change in treatment, compared with the current approach of no platelet function testing and no change in treatment. The model considers how being classified as aspirin resistant based on a test of platelet function and subsequently adding or changing treatment may lead to a reduced risk of experiencing a MACE, but may also increase the risk of major bleeding. Owing to the large amount of clinical uncertainty identified by the systematic review of prognostic and diagnostic utility (see *Chapter 5*), this economic model evaluates a hypothetical PFT and hypothetical change of treatment in patients with existing cardiovascular disease or CVD, considers whether or not such a test would be cost-effective and investigates the main factors affecting cost-effectiveness. An overview of the key characteristics of the cost-effectiveness analysis is shown in *Box 1*.

BOX 1 Characteristics of the cost-effectiveness analysis

Intervention Hypothetical aspirin-specific PFT or global PFT where patients are receiving aspirin as the only antiplatelet therapy at the time of testing, followed by a hypothetical change of treatment if, based on the test, patients are defined as aspirin resistant. Possible treatment options are (1) increase dose, (2) increase frequency (split dose), (3) combination therapy, (4) change treatment (alternative monotherapy).

Comparator No assessment of platelet function and no change of treatment (current practice).

Population Cohort of patients with stable CAD who are receiving aspirin as the sole antiplatelet agent (monotherapy); 66% male and aged 60 years.

Time frame Lifetime time horizon; 1-year time cycle.

Perspective NHS/PSS.

Effects MACEs and major bleeds.

Costs Costs associated with platelet function testing, changing antiplatelet therapy and treating patients who have experienced a fatal or non-fatal MACE or major bleed.

Outcomes Mortality, quality of life, QALYs.

Assessment of cost-effectiveness Cost per additional QALY gained.

QALY, quality-adjusted life-year.

Methods

Model description

A speculative economic model developed as a decision tree combined with a Markov model was built in TreeAge Pro® (TreeAge Software, Inc., Williamstown, MA, USA) to estimate the cost-effectiveness of platelet function testing with the option of change in treatment compared with no testing and no change in treatment (current treatment). The population considered was patients with stable CAD on aspirin monotherapy. Based on clinical judgement the patient cohort was assumed to be aged 60 years and 66% male, in keeping with studied populations included in this report. The time horizon of the model was patient lifetime and the model was therefore run for 41 years. Mortality data were weighted to take into account the greater proportion of men with the disease. A time cycle of 1 year was chosen, as it was felt that a shorter and more detailed time period would not be required owing to the speculative nature of the model and data inputs. The model structure is shown in *Figure 60*.

In the decision tree, for both treatment options of testing with a change in treatment and no testing and no change in treatment (current treatment), the cohort was separated at a chance node based on whether patients were identified as aspirin resistant or aspirin sensitive. The Markov model followed on from each of these branches. Therefore, patients identified as aspirin resistant followed one model pathway, while those identified as aspirin sensitive followed a separate model pathway. However, the subsequent model pathways were the same for all test and treatment options.

The entire cohort began in the state 'event free (on treatment)'. From this health state, patients moved along a pathway where they could remain in this health state, die from other causes or experience a fatal or non-fatal MACE or major bleed. Depending on the events experienced during this initial pathway, patients moved to the subsequent health states 'post event' after a non-fatal MACE, 'event free (off treatment)' after suffering a non-fatal major bleed and having antiplatelet therapy discontinued, or 'dead', or remained in the health state 'event free (on treatment)'. Once in a 'post event' health state, the patient either remained in this state or died, with the mortality risk higher as a result of having suffered a previous MACE. The pathway for 'event free (off treatment)' was the same as for those who were event free and on treatment, but with adjustments to event rates taking into account whether or not treatment was being taken.

The intervention option assumed that all patients received a hypothetical PFT with a one-off cost, and, if defined as aspirin resistant, had their treatment changed with an associated additional cost. The treatment change could decrease the risk of a MACE but could also increase the risk of a major bleed. If a major bleed occurred, all antiplatelet therapy was discontinued and the risk of a future MACE increased to a higher level. Those who were defined as aspirin sensitive did not have their treatment changed. In the current treatment option, there was no testing (although the differentiation between aspirin resistant and aspirin sensitive was maintained) and aspirin monotherapy was continued, unless a major bleed caused a discontinuation of treatment. In the base case, the model assumed that those defined as aspirin resistant had an overall average raised risk of MACEs and an overall average benefit from a change in treatment.

The model was designed to estimate costs, from the perspective of the NHS and PSS, and outcomes in terms of quality-adjusted life-years (QALYs) gained by each arm of the model, with costs and QALYs accumulated depending on the transitions between health states. The difference between the costs, incidence of health outcomes and impact on quality of life and mortality between treatment options was used to estimate the incremental costs and effects of applying a hypothetical PFT and treatment change. The model also attempted to incorporate uncertainty in model parameters by incorporating probability distributions for the majority of input parameters. All costs were for a price year of 2011–12, and were inflated to this price year where appropriate. Costs and QALYs were discounted at a rate of 3.5% per annum.

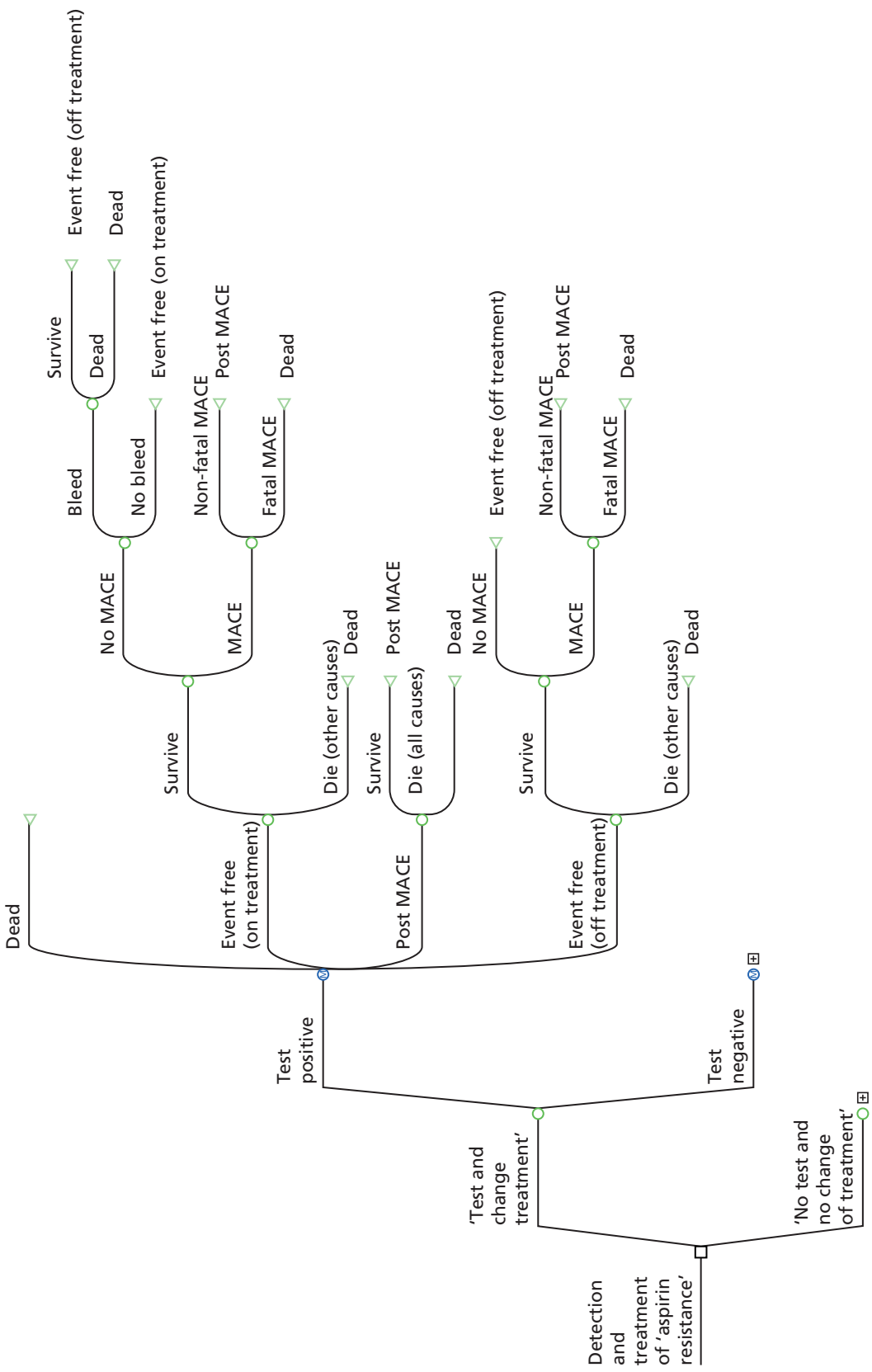

FIGURE 60 Decision tree and Markov model used to assess the cost-effectiveness of platelet function testing plus change of treatment.

Estimation of model parameters

The parameters and sources used in the model are summarised in *Tables 76–78*. Given the range of data required to populate the model, a variety of approaches were used to identify parameter estimates. First, systematic reviews were undertaken to identify parameter estimates reported in the existing literature. However, as described in *Chapter 5* and in *Systematic review of cost-effectiveness studies*, the prognostic and diagnostic utility data available were associated with heterogeneity and uncertainty and no relevant published economic evaluations were identified. Several parameter estimates were sourced from clinical papers, for example the risk of major bleeding, and utility values for health states were obtained from previous modelling studies in cardiovascular disease. However, as a result of the clinical uncertainty in this area, the majority of the data in this model are based on expert opinion and assumptions. As the model is speculative, the base-case result aims to present cost-effectiveness for a hypothetical test and treatment strategy which reduces the risk of MACEs in aspirin-resistant patients. The values used in the sensitivity analysis aim to test all of the assumptions and present different scenarios to show when a test and change in treatment may or may not be cost-effective.

TABLE 76 Base-case clinical data and assumptions included in the economic model

Probabilities	Value	Distribution	Source
Testing positive for aspirin resistance	0.225	Beta $\alpha = 2, \beta = 6.89$	Estimate from clinical review (see *Tables 4*, *15*, *26*, *37*, *48*, *58* and *67*)
MACE (aspirin sensitive) (1 year)	0.05	Beta $\alpha = 2, \beta = 38$	Assumption from expert opinion
Proportion of MACEs as stroke	0.2	Beta $\alpha = 2, \beta = 8$	Assumption from expert opinion
Fatal MACE	0.09	Beta $\alpha = 2, \beta = 20.2$	Assumption from expert opinion
Major bleed (1 year)	0.001	Beta $\alpha = 2, \beta = 1998$	Antithrombotic Trialists' Collaboration (2009)[4]
Death from a major bleed	0.125	Beta $\alpha = 2, \beta = 14$	Assumption from expert opinion
Relative risks			
Relative risk applied to baseline MACE risk to calculate risk if aspirin resistant (note the reciprocal was applied to the baseline risk)	0.66	Beta $\alpha = 3.88, \beta = 2$	Assumption from expert opinion
Relative risk of a major bleed with a change in treatment	1.4	Beta (reciprocal value of 0.71 used) $\alpha = 5, \beta = 2$	Assumption using data from Eikelboom (2012)[5]
Relative risk of impact of change in treatment on MACE	0.8	$\alpha = 8, \beta = 2$	Assumption from expert opinion
Standardised mortality ratio			
Post MACE	2.7	Log normal $\sigma = 0.036$	Bronnum-Hansen (2001)[270,271]

TABLE 77 Unit costs used in the model

Variable	Cost (£)	Source
Test for aspirin resistance	50	Assumption (minimum cost)
Antiplatelet therapy (aspirin) (annual)	11	BNF (2013)[272]
Hypothetical additional treatment if aspirin resistant (annual)	30	BNF (2013)[272]
Major bleed	4287	Weighted cost of GI bleed from NHS reference costs 2011–12[273] (75%) and acute stroke cost (25%)
Acute MI	5487	Robinson (2005)[274]
Acute stroke	11,020	Youman (2003)[275]
Long-term MI (annual)	2196	Robinson (2005)[274]
Long-term stroke (annual)	2721	Youman (2003)[275]
Fatal MI	2359	Greenhalgh (2011)[276]
Fatal stroke	9326	Greenhalgh (2011)[276]

BNF, *British National Formulary*.

TABLE 78 Utility data used in the model

Event/health state	Value	Beta distribution	Source
Post MI	0.88	$\alpha = 285.94$, $\beta = 38.99$	Cooper (2008)[277]
Acute MI	0.76	$\alpha = 2$, $\beta = 14.67$	Ward (2007)[278]
	(distribution for decrement of 0.12)		
Post stroke	0.63	$\alpha = 91.15$, $\beta = 53.53$	Ward (2007)[278]
Acute stroke	0.55	$\alpha = 2$, $\beta = 23$	Cooper (2008)[277]
	(distribution for decrement of 0.08)		
One-off disutility of a bleed	–0.1426	$\alpha = 2$, $\beta = 12.03$	Greenhalgh (2011)[276]

Clinical parameters Many of the clinical parameters in the model were not known with any certainty, therefore values were estimated after discussion with clinical experts in the study team, and wide probability distributions were applied to these estimates to reflect the extent of uncertainty. The clinical parameter values can be found in *Table 76*.

The base-case value for the proportion defined as aspirin resistant varied considerably between tests and studies. Given this high variation across studies included in the prognostic utility review, an arbitrary value of 22.5% was used in the base case, in keeping with the range of values identified. This parameter was tested across a wide range of values in the sensitivity analysis. The annual risk of a MACE in clinically stable patients who were defined as aspirin sensitive and on aspirin was assumed to be 5%. An overall baseline risk of MACEs in aspirin-resistant patients was difficult to determine from the prognostic review, therefore an assumption was made for the base case that this risk would be, on average, higher. A base case value of 7.5% was chosen (assumption from expert opinion). In order to vary this value in both the deterministic

and probabilistic sensitivity analysis (PSA), the risk of a MACE in aspirin-sensitive patients was divided by a relative risk to give the higher risk estimate for aspirin-resistant patients. For the base case a relative risk of 0.66 was used to obtain a risk of 7.5%. The model was constructed to allow an assumption of no association between the result of the PFT and the risk of MACEs (and relative risk is equal to 1), with a hypothesis that either platelet function as measured by the test is not related to the clinical outcome, the test does not discriminate well or there is little difference in the risks between those defined as aspirin resistant and those defined as aspirin sensitive. In the PSA, this relative risk was sampled from a distribution in two stages. A uniform distribution was used to determine a number between 0 and 1. For all values between 0 and a certain proportion, x, sampling would be from a beta distribution around the relative risk of 0.66. For values sampled between x and 1, the risk of MACEs in aspirin-resistant and aspirin-sensitive patients would be the same, and the relative risk would be 1. Therefore the smaller the fixed proportion x, the more likely there would not be an increased risk of events in patients defined as aspirin resistant.

A hypothetical change in treatment for aspirin-resistant patients was assumed to have some effect in the base-case model, and a relative risk of 0.8 was used (assumption from expert opinion). As described previously for the risk of MACEs in aspirin-resistant patients, in the PSA the distribution of the relative risk for treatment effect was constructed so that a value of no effect could be applied for a fixed proportion, and an assumption of no effect of a change in treatment could be tested. The annual risk of major bleeding due to antiplatelet therapy in aspirin-sensitive patients was set at 0.01% (assumption from expert opinion). To account for a change in antiplatelet therapy, and a possible increase in major bleeds, a relative risk was applied to increase this risk of bleeding. As the change in treatment was hypothetical, a value of 1.4 was chosen, taking into account evidence on the impact of adding clopidogrel to aspirin or doubling the dose of an antiplatelet agent.[5] If an aspirin-resistant or aspirin-sensitive patient was taken off all antiplatelet therapy as a result of a major bleed, the patient's risk of a further bleeding event (in an 'off treatment' health state) was assumed to be zero. Although there will be a very small risk of a major bleed in reality, this will be lower than the aspirin estimate of 0.01%, and is therefore considered to be negligible with regards to impact on the model results.

It was estimated that 9% of major bleeds would result in death, from the assumption that 1 in 10 events would be fatal. Probability of death from a major bleed was assumed to be 12.5%, assuming that 25% of major bleeds were intracranial haemorrhage (ICH) and that half of these were fatal.

Mortality Sex-specific life tables were used to determine the probability of death for all ages. The risk of death was adjusted to ensure there was no double counting of cardiovascular disease deaths, using data from the Office for National Statistics on the proportion of deaths by cardiovascular disease causes.[279] The model assumed that there was an increased risk of death once in the postevent health state and this was applied to the probability of death.

Resource use and costs No published data were available on the cost of any of the PFTs, and as the test in the model was deemed to be hypothetical, an arbitrary cost of £50 was used, with alternative higher costs included in the sensitivity analysis. The cost of a change in treatment was also unknown as there are a number of potential changes in treatment that could be made, which may increase costs greatly or not at all. In the base-case analysis, the cost of generic clopidogrel (£30 a year, 75 mg once daily) in addition to aspirin was used. This was varied in the sensitivity analysis to consider the approximate cost of adding a newer branded drug such as prasugrel (£600 a year, assuming a body weight of > 60 kg and a daily dose of 10 mg) or ticagrelor (£702 a year, assuming 90 mg twice daily). The cost of aspirin for a year (£11) applied to all patients in the model except for those who had all antiplatelet treatment discontinued. All drug costs were obtained from the *British National Formulary* (BNF).[272] The acute and long-term costs of stroke were obtained from a UK study collecting primary data,[275] and acute and long-term costs of MI were obtained from a previous cardiovascular disease model.[274] The source of fatal stroke and MI costs

was an economic modelling study concerning other antiplatelet therapy for cardiovascular disease.[276] The exact split between stroke and MI events is not known, therefore an estimate of 20% stroke and 80% MI was used, and costs weighted accordingly. The cost of a major bleed assumed that 75% of bleeds were GI and 25% were ICH. NHS reference costs[273] provided the cost of a GI bleed, and the cost of an acute stroke was assumed for an ICH. No long-term costs were attributed to bleeds, and this underestimated the cost; however, it was assumed that 50% of those who suffered an ICH died, and the initial risk of a bleed was very low. The perspective adopted for the model was that of the NHS/PSS, and a price year of 2011–12 was applied. Unit costs used in the model can be found in *Table 77*.

Estimation of quality-adjusted life-years Outcomes were measured in QALYs. Age-related general population utilities from the European Quality of Life-5 Dimensions (EQ-5D) provided the baseline values for quality of life,[280] with quality of life decreasing with increasing age. Utility values were given for all health states. When a MACE occurred within the model, a utility for an acute event was applied for the first year, with further, slightly higher utility applied in the postevent health state. The lower utility value for an acute health state was applied as a decrease in utility which was subtracted from the postevent utility value. The weighting of stroke to MI events used for MACE costs was also utilised here. Values were applied multiplicatively; therefore, the value for the state of the clinical event was multiplied by the value for the age. Where a major bleed occurred, a one-off reduction in utility was applied. The utility values were obtained from previous studies,[276–278] and entered into the model as beta distributions (see *Table 78*).

Model assumptions

Owing to the speculative nature of this model, a number of assumptions were made regarding the model structure and input parameters. In the base case it was assumed that, based on a hypothetical test of platelet function, patients could be defined as aspirin resistant (having insufficient platelet function inhibition) or aspirin sensitive, and that patients defined as aspirin resistant have a higher average risk of MACEs than those defined as aspirin sensitive. This higher risk could, on average, be subsequently reduced with a hypothetical change in treatment. MACEs only included fatal and non-fatal stroke and MI, with the assumption that MI was the event occurring 80% of the time. Recurrent events were not included in the model, and once a MACE occurred, the patient moved into a postevent state with a lower quality of life and ongoing costs. Furthermore, it was assumed that a change in antiplatelet therapy would increase the risk of a major bleed (assumed to be a GI bleed or ICH). If a major bleed of this type occurred anywhere in the model, a one-off cost and reduction in quality of life was applied and all antiplatelet therapy ceased, thus increasing the risk of a MACE in the future. The model did not take into account the possible ongoing costs or additional reduction in quality of life from the starting state of stable CAD; however, this applied to all treatment options. The cost of a change in treatment was assumed to be the additional cost of clopidogrel in the base case, with newer, more expensive drugs included in the sensitivity analysis. Although these drugs are more appropriate for acute coronary syndromes rather than stable disease, it was felt that these prices would be a reasonable approximation of a newer drug which may be available for stable patients.

Assessment of cost-effectiveness

The analysis was designed to generate the cost per additional QALY gained of performing a PFT and modifying treatment based on the test findings. In order to ensure consistency in the model, an additional arm (test and no change of treatment) was also included in the economic model. However, this is not a feasible clinical option, because if no change in treatment is intended based on the test result, then there is no reason to test. As the only difference between this arm and the standard care (no test and no change of treatment) arm is the cost of the test, it served as a consistency check for the functioning of the model. Results for this option are not presented in this report.

Where available, data were entered into the model as distributions in order to fully incorporate the uncertainty around parameter values so that a PSA could be undertaken. The PSA was run with 1000 simulations and cost-effectiveness planes and acceptability curves were produced. Owing to

the speculative nature of the model and the large amount of uncertainty around many of the model variables, beta distributions were applied to those parameters where neither a reasonable point estimate nor an actual distribution was known. The beta distributions were constructed in order to represent the greatest amount of uncertainty and were presented in *Tables 76* and *78*. The currently accepted, lower National Institute for Health and Care Excellence threshold of £20,000 per QALY gained is used to assess cost-effectiveness.[281]

Deterministic sensitivity analysis

A sensitivity analysis was performed to determine the impact of changing key parameters on the model results. Therefore, many of the model parameters were subject to one- and two-way sensitivity analysis, using hypothetical increases or decreases, to determine the key drivers of the model results. Parameters varied included the costs of the test and change in treatment, event costs, the probability of testing positive for aspirin resistance, changes to the risk of MACEs with aspirin resistance, fatality rate and composition of MACEs (in terms of proportions of stroke and MI) and reduction in risk with a change in treatment. Parameters associated with major bleeding were also varied. A 'worst-case scenario' was also run, which assumed that those who were aspirin resistant did not have a higher risk of MACEs, a change in treatment was not effective, the test cost was £1000, the change in treatment cost £702 a year and the risk of major bleeding increased by a relative risk of 2.8.

Results

This section presents the results of the cost-effectiveness analysis.

The base-case results shown in *Table 79* indicate that the intervention of 'test and change treatment' is cost-effective, and 'no test and no change of treatment' (standard care) is absolutely dominated, i.e. is more costly and less effective. This analysis assumed that for aspirin-resistant patients, there was an overall higher average risk of MACEs and an overall average reduction in MACE risk with a change in treatment. Results from the PSA show that although there is a wide spread of points, the majority are in the south-east quadrant of the cost-effectiveness plane (*Figure 61*), indicating dominance of the 'test and change treatment' strategy. The cost-effectiveness acceptability curve (*Figure 62*) also shows that the intervention has a high probability of being cost-effective at all willingness-to-pay thresholds.

TABLE 79 Base-case cost-effectiveness analysis

Strategy	Mean cost (£)	Cost difference (£)	Mean QALYs	QALY difference	ICER (cost per QALY)
'No test and no change of treatment'	13,256		9.6607		
'Test and change treatment'	12,940	–316	9.7370	0.0763	Dominant

ICER, incremental cost-effectiveness ratio.

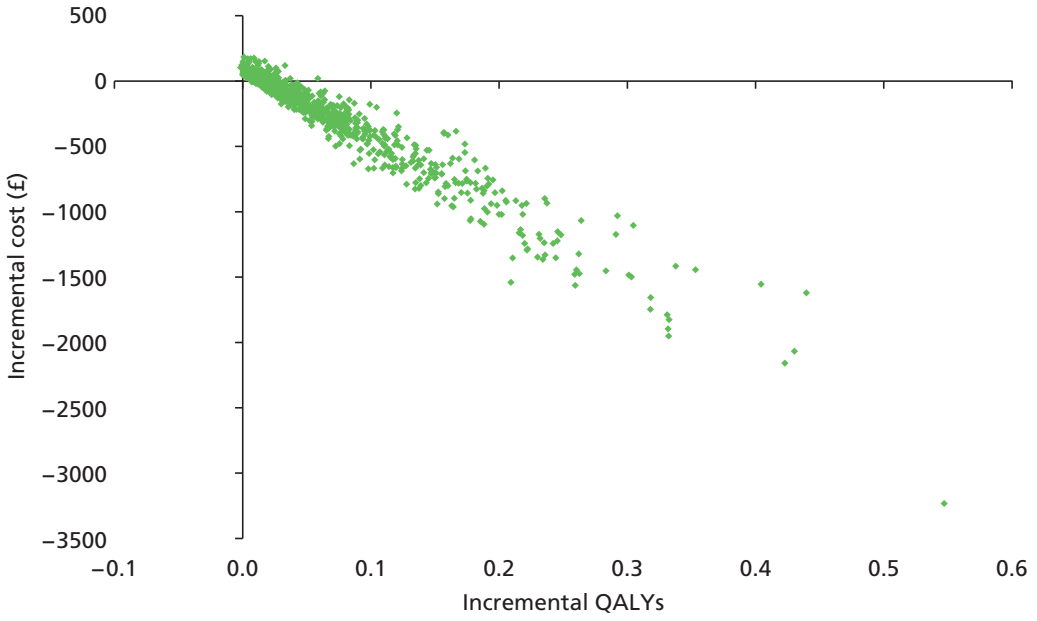

FIGURE 61 Cost-effectiveness plane of 'test and change treatment' vs. 'no test and no change in treatment': base-case analysis.

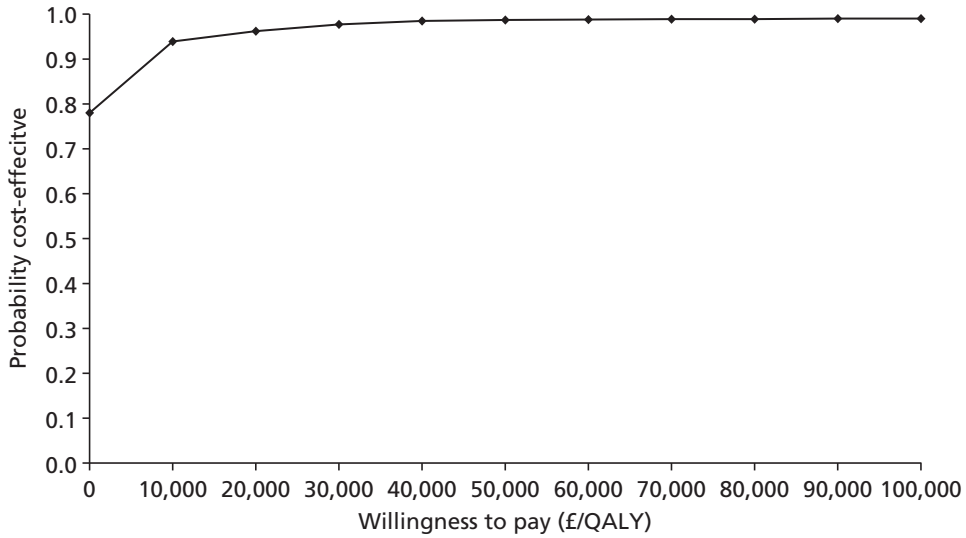

FIGURE 62 Cost-effectiveness acceptability curve of 'test and change treatment' vs. 'no test and no change in treatment': base-case analysis.

Sensitivity analysis

Tables 80 and *81* present the results of one-way sensitivity analysis of key model parameters, where each variable was varied with all other parameters fixed at base-case values.

Most of the clinical variables did not change the overall results where the 'test and change treatment' was cost-effective and dominant over standard care (see *Table 80*). Decreasing the percentage that test positive for aspirin resistance to only 1% meant that the intervention was no longer dominant, but was still cost-effective at approximately £10,000 per QALY gained. Neither changing the nature of MACEs in terms of proportions of strokes and MIs and percentage of fatal MACEs, nor changing the risk and fatality rate from bleeds, had any impact on the results. Reducing the effectiveness of the treatment change (in terms of preventing MACE) did change the magnitude of the cost and QALY differences; however, only an ineffective treatment changed the

TABLE 80 Result of the one-way sensitivity analysis of 'test and change treatment' vs. 'no test and no change in treatment' (standard care): clinical parameters

Results	Cost difference vs. standard care (£)	QALY difference vs. standard care	ICER for 'test and change treatment' (cost per QALY gained) (£)
Base-case result	–316	0.0763	Dominant
Sensitivity analysis			
Testing positive for aspirin resistance			
0.5	–763	0.1696	Dominant
0.1	–116	0.0346	Dominant
0.01	34	0.0034	9951
MACE risk if aspirin resistant			
0.05 (no change)	–263	0.0704	Dominant
0.10 (risk doubled)	–328	0.0754	Dominant
Fatal MACEs			
0.18 (doubled)	–278	0.0858	Dominant
0.045 (halved)	–335	0.0715	Dominant
Proportion of MACEs as stroke			
0.4 (doubled)	–348	0.0821	Dominant
0.5 (equal split)	–364	0.0850	Dominant
Major bleed on aspirin			
0.01 (risk increased tenfold)	–267	0.0617	Dominant
Death from a major bleed			
0.25 (doubled)	–317	0.0754	Dominant
Relative risk of a major bleed with a change in treatment			
2.8 (risk doubled)	–305	0.0726	Dominant
1.2 (risk reduced)	–317	0.0768	Dominant
Relative risk of a MACE with change in treatment			
0.9	–94	0.0357	Dominant
1	108	–0.0008	Dominated by no test and no change of treatment
No change in MACE risk if aspirin resistant and no reduced risk of MACEs with change in treatment	121	–0.0010	Dominated by no test and no change of treatment

ICER, incremental cost-effectiveness ratio.

TABLE 81 Result of the one-way sensitivity analysis of 'test and change treatment' vs. 'no test and no change in treatment' (standard care): cost parameters and time horizon

Results	Cost difference vs. standard care (£)	QALY difference vs. standard care	ICER for 'test and change treatment' (cost per QALY gained) (£)
Base-case result	–316	0.0763	Dominant
Sensitivity analysis			
Cost of test for aspirin resistance			
£100 (doubled)	–266	0.0763	Dominant
£500 (increased tenfold)	134	0.0763	1760
£1000 (high value)	634	0.0763	8314
Cost of hypothetical additional treatment			
£600 (annual cost of prasugrel)	870	0.0763	11,410
£702 (annual cost of ticagrelor)	1083	0.0763	14,192
All event costs **increased** by 50%			
All events	**–529**	**0.0763**	Dominant in all cases
Major bleed	–314	0.0763	
Acute MI	–345	0.0763	
Acute stroke	–330	0.0763	
Long-term MI	–444	0.0763	
Long-term stroke	–356	0.0763	
Fatal MI	–317	0.0763	
Fatal stroke	–317	0.0763	
All event costs **decreased** by 50%			
All events	**–100**	**0.0763**	Dominant in all cases
Major bleed	–318	0.0763	
Acute MI	–287	0.0763	
Acute stroke	–301	0.0763	
Long-term MI	–185	0.0763	
Long-term stroke	–275	0.0763	
Fatal MI	–314	0.0763	
Fatal stroke	–314	0.0763	
Time horizon (years)			
5	–50	0.0059	Dominant
10	–168	0.0191	Dominant
20	–304	0.0495	Dominant

ICER, incremental cost-effectiveness ratio.

result in favour of standard treatment. This was more apparent when it was assumed that there was no baseline increased risk of MACEs and no impact of testing and treating.

Table 81 presents the sensitivity analysis around the cost parameters and time horizon of the model. Increasing or decreasing all of the event costs, or each one separately by 50%, did not change the overall result. However, the model was sensitive to the cost of a PFT, although the 'test and change treatment' option was still cost-effective even at a value of £1000 per test. The cost of the hypothetical treatment also had an impact, with the costs of newer, branded antiplatelet therapies giving incremental cost-effectiveness ratios (ICERs) of over £10,000 per QALY but still below the £20,000-per-QALY threshold. Decreasing the time horizon of the model to 5, 10 and 20 years did reduce the cost and QALY differences, but 'test and change treatment' was still cost-effective.

Table 82 shows the results of the 'worst-case scenario' where, in the 'test and change treatment' option, costs of the PFT and a change in treatment were higher, those who were aspirin resistant did not have a higher risk of MACEs than those who were aspirin sensitive, a change in treatment was not effective and the risk of major bleeding was higher. Here, the 'test and change treatment' option is dominated by standard care, and costs £2585 more per patient with a loss of 0.0043 QALYs.

Two-way sensitivity analyses were also undertaken to assess the impact of changing two key variables at the same time (*Table 83*). The cost of the PFT and change in treatment were both increased at the same time, which changed the result from dominance to a positive ICER. Once both test and treatment costs were in the region of £600–700 each, then the intervention was no longer cost-effective, assuming a £20,000-per-QALY threshold.

TABLE 82 'Worst-case scenario' sensitivity analysis

Strategy	Mean cost (£)	Cost difference (£)	Mean QALYs	QALY difference	ICER (cost per QALY)
'No test and no change of treatment'	12,445		9.8073		
'Test and change treatment'	15,030	2585	9.8030	–0.0043	Dominated by no test and no change of treatment

TABLE 83 Two-way sensitivity analysis of 'test and change treatment' vs. 'no test and no change in treatment' (standard care)

Cost of test (£)	Cost of change in treatment (£)	Cost difference vs. standard care (£)	QALY difference vs. standard care	ICER for 'test and change treatment' (cost per QALY gained) (£)
50	30	–316	0.0763	Dominant
125	125	–43	0.0763	Dominant
250	250	342	0.0763	4276
375	375	727	0.0763	9090
500	500	1112	0.0763	13,904
625	625	1498	0.0763	18,719
750	750	1883	0.0763	23,533
875	875	2268	0.0763	28,346
1000	1000	2653	0.0763	33,160

Finally, PSA was undertaken where a variable related to the presence of a reduction in MACE risk due to a change in treatment was altered. In the base case, it was assumed there would be some impact of treatment. However, the model was constructed so that, in a PSA, the variable for risk reduction could hold the value 1 (no change) for a given proportion, x, with the assumption that for this proportion x of patients, the treatment had no impact on MACE risk. The first PSA set this value x to 0.5 and the results can be seen in *Figures 63* and *64*. This analysis reduces the probability of 'test and change treatment' being cost-effective at the £20,000-per-QALY threshold to 48% – no longer a cost-effective option. A further PSA was run with 50% of patients getting no benefit from treatment and the cost of a change in treatment set to £702 a year, and this further reduced the probability of cost-effectiveness to 24% (*Figures 65* and *66*). Finally, a PSA was undertaken to consider a scenario where 50% of all patients defined as aspirin resistant had no increase in MACE risk and 50% of all those defined as aspirin resistant do not benefit from a change in treatment (*Figures 67* and *68*). Again, the 'test and change treatment' option is not cost-effective, and has a 50% probability of being cost-effective at £20,000 per QALY.

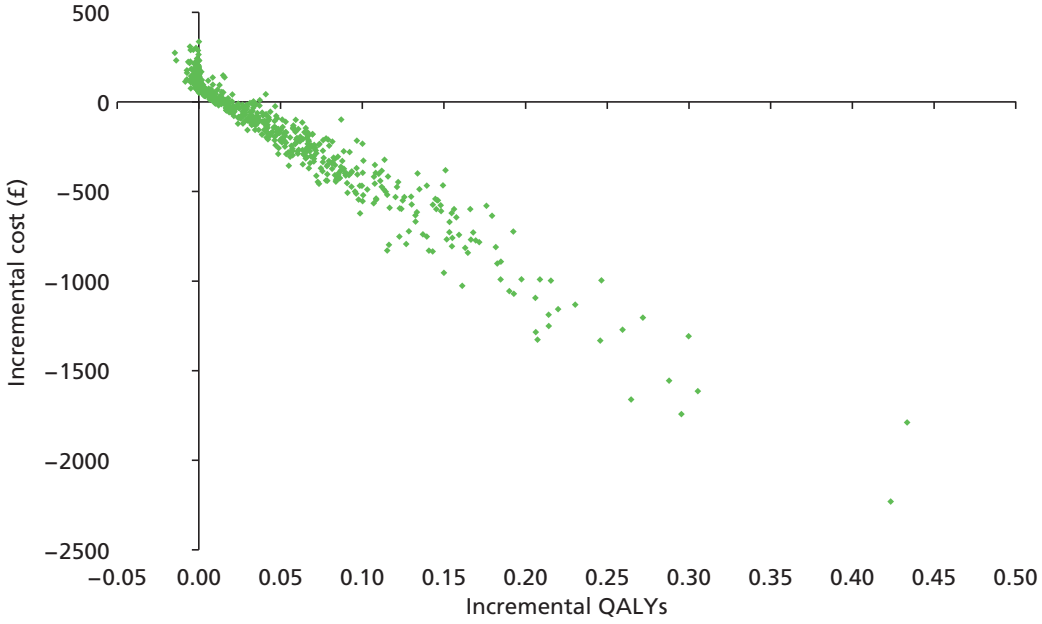

FIGURE 63 Cost-effectiveness plane of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients have no change in MACE risk with a change in treatment.

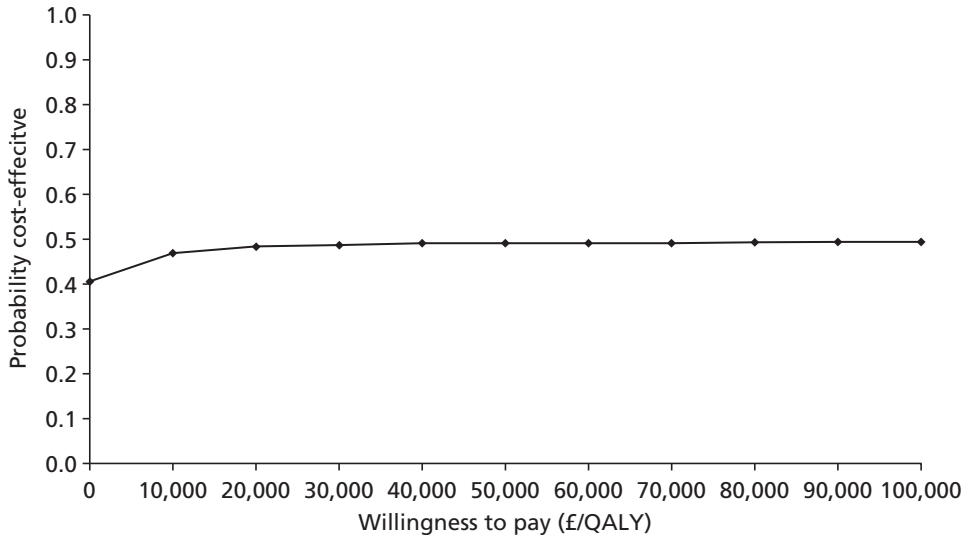

FIGURE 64 Cost-effectiveness acceptability curve of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients have no change in MACE risk with a change in treatment.

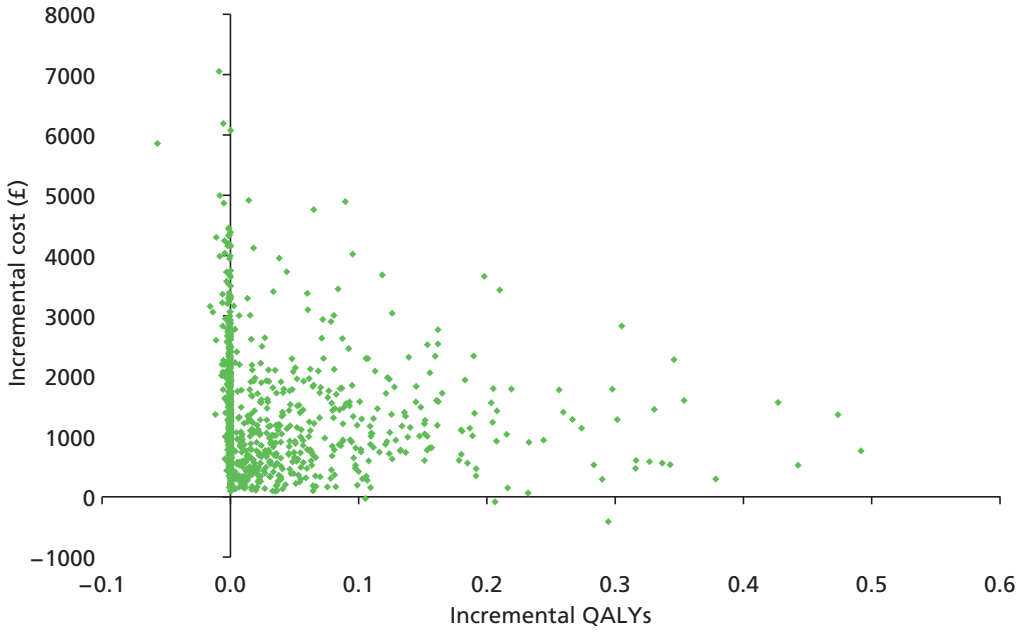

FIGURE 65 Cost-effectiveness plane of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients have no change in MACE risk with a change in treatment and change in treatment costs are £702.

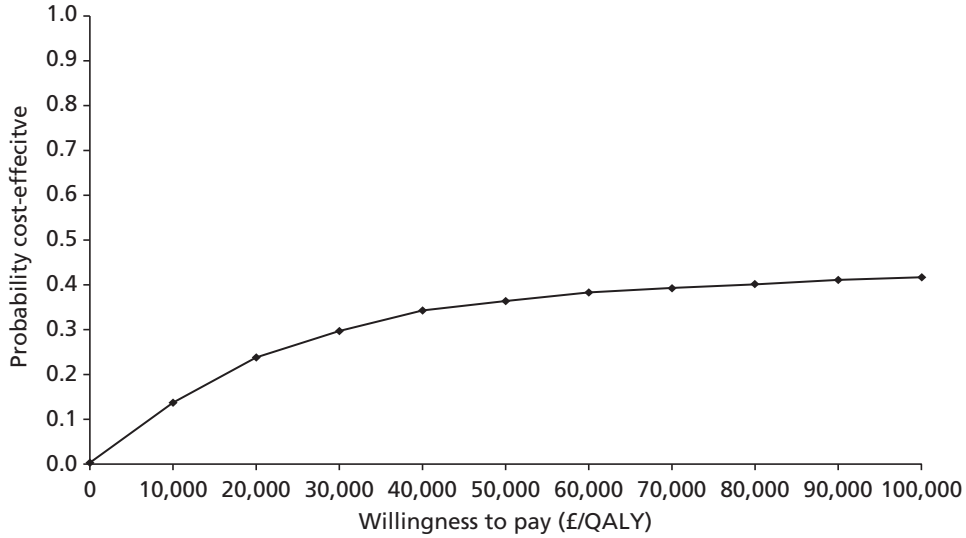

FIGURE 66 Cost-effectiveness acceptability curve of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients have no change in MACE risk with a change in treatment and change in treatment costs are £702.

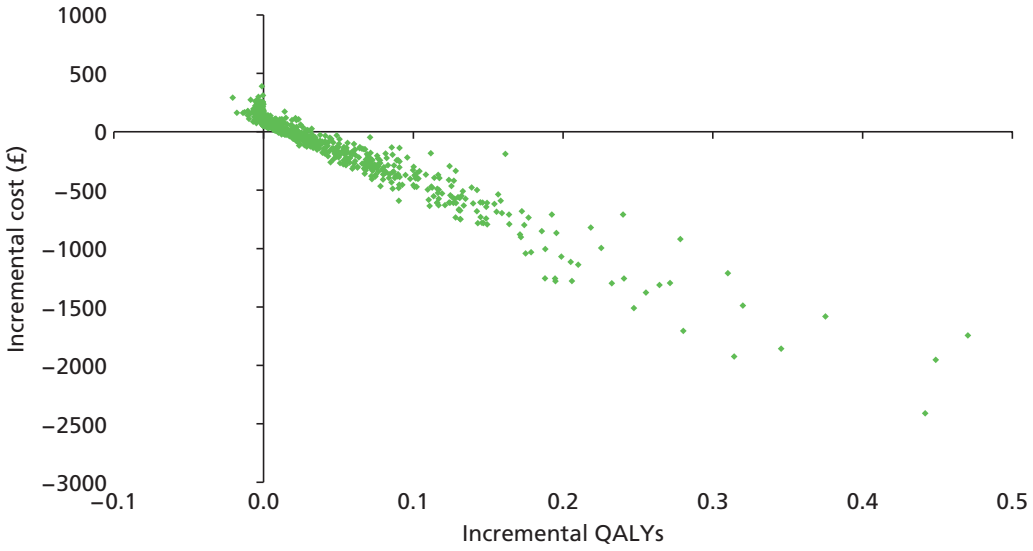

FIGURE 67 Cost-effectiveness plane of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients do not have elevated MACE risk and 50% have no change in MACE risk with a change in treatment.

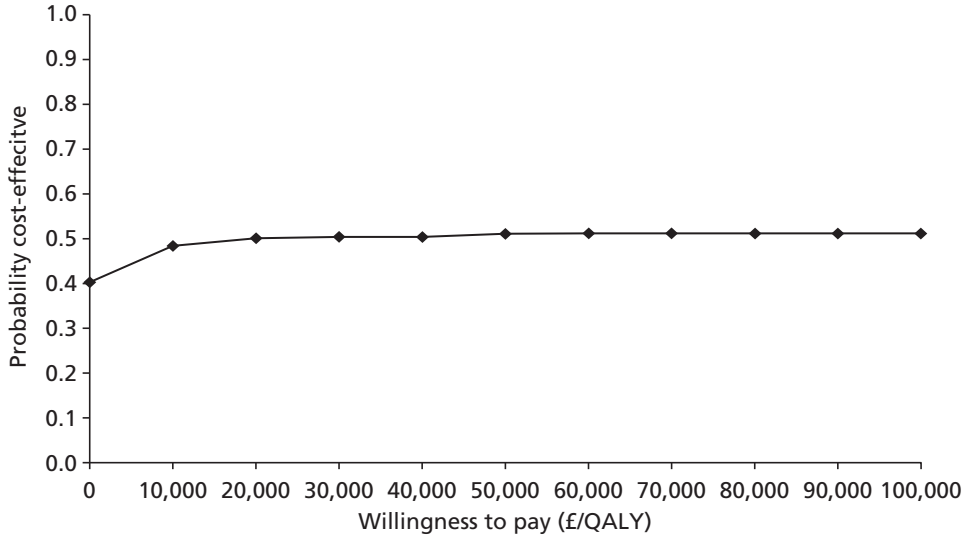

FIGURE 68 Cost-effectiveness acceptability curve of 'test and change treatment' vs. 'no test and no change in treatment': 50% of patients do not have elevated MACE risk and 50% have no change in MACE risk with a change in treatment.

Cost-effectiveness discussion

The results of the cost-effectiveness analysis for the base-case values indicate that if a PFT were available that was able to accurately identify individual patients who, while receiving aspirin therapy, were at higher risk of an adverse clinical outcome than other patients, and a subsequent change in treatment reduced the risk of MACEs in such individuals, this would be a highly cost-effective strategy, as long as the costs of testing and a change in treatment were not excessively high. This result was robust with regards to most model variables. However, this result changes when values of important (and currently unknown) variables are varied. Within the sensitivity analyses, results were sensitive to the proportion defined as 'aspirin resistant', and the availability of an effective treatment alternative for patients on aspirin discovered to be at an elevated risk of MACEs. Factors that adversely affect the cost-effectiveness of testing and changing therapy include only a very small proportion of patients being defined as 'aspirin resistant', if the cost of testing is high and a change in treatment is costly and/or not highly effective. This is exemplified by the 'worst-case scenario' sensitivity analysis, which demonstrates that if an expensive test cannot identify individuals at a higher risk of clinical events and a costly change in treatment does not reduce the risk of MACEs but increases the risk of bleeding, then the 'test and change treatment' option results in much higher costs and a reduction in QALYs, and is therefore not cost-effective.

A key strength of this analysis is that this is the first economic model to consider the cost-effectiveness of testing for and treating patients defined as 'aspirin resistant', and it can illustrate the key variables that have an impact on the results. Although few good-quality data currently exist to populate the model, a model structure exists for reanalysis once additional data become available. The main limitation is the highly speculative nature of the model and the uncertainty around parameter values resulting from the absence of evidence. This has been addressed where possible by the deterministic sensitivity analysis that has been undertaken and by applying the greatest amount of uncertainty around many of the model parameter values. However, as most distributions have been assumed, there should be caution in interpreting the results of the PSA, as there may be biases in quantifying the uncertainty and the direction of this bias is unknown.

The model assumes that patients at elevated risk of cardiovascular outcomes can be accurately identified by a test, i.e. that PFTs are perfectly accurate in discriminating those patients with and without 'abnormal' platelet function and that 'abnormal' platelet function is associated with a risk of cardiovascular outcomes. This assumption was, in part, explored in sensitivity analyses. The preferred approach in economic models for diagnostic testing is to consider test performance in terms of sensitivity and specificity, requiring prevalence data and a reference standard test, which do not exist for PFTs. In the absence of information, a perfect test has been assumed, and the probability of being 'aspirin resistant' varied in the sensitivity analysis.

The model structure may also be viewed as somewhat simplistic, with no recurrence of clinical events and no increase in the risk of events over time. However, if the model had included both features, a reasonable 'test and change treatment' strategy is likely to appear even more cost-effective. This model is for stable CAD patients only, and an additional model was not constructed for ACS patients on dual therapy. As this patient group is likely to have an even higher risk of MACEs, the results are likely to have shown similar levels of cost-effectiveness.

Summary

- Currently, there is no existing economic evidence on the cost or cost-effectiveness of platelet function testing for 'aspirin resistance', which is surprising considering the amount of research identified by the systematic review of prognostic/diagnostic utility and the degree of debate around this topic.
- This is the first model to attempt to estimate the cost-effectiveness of a 'test and change treatment' strategy for 'aspirin resistance'.
- The model is highly speculative owing to the heterogeneity and uncertainty around the prognostic/diagnostic utility of PFTs available to populate the model and contains a number of assumptions.
- If a PFT can accurately identify patients at higher risk of adverse clinical outcomes while receiving aspirin therapy as the sole antiplatelet agent, and patients have an effective treatment change, then a 'test and change treatment' option is very likely to be cost-effective. Conversely, if a PFT cannot identify these patients, and a treatment change is not effective in reducing MACE risk, then a 'test and change treatment' strategy is not cost-effective.
- The parameters with the greatest impact on model results are the proportion of patients who are correctly identified as having a high risk of adverse clinical outcomes, the effectiveness of a change in treatment if 'aspirin resistant', the cost of a test and the cost of a change in treatment.
- The model requires more robust data on the association between a designation of 'aspirin resistance' and the risk of adverse clinical outcomes, PFTs that can accurately define patients as 'aspirin resistant' and appropriate alternative therapy options for those at higher risk of adverse clinical outcomes.

Chapter 7 Discussion

Summary of results: prognostic utility review

Monotherapy

For assessment of the prognostic utility of PFTs in patients receiving aspirin as a monotherapy (at the time of testing), a majority of patients in all studies included were considered to have stable disease. There was considerable heterogeneity in other population characteristics (e.g. smoking, diabetes), as well as differences relating to treatment (e.g. aspirin dose), tests and testing procedures used, threshold for classifying patients as 'aspirin resistant', range and definition of clinical outcomes recorded and length of patient follow-up. There was a lack of detail in reporting of quality criteria and no study reported all the items considered to be important. Lack of detail related in particular to blinding (of those undertaking PFTs to patient characteristics, or blinding of outcome assessors), loss-to-follow-up information and level of compliance with aspirin treatment. There was no consistent reporting of outcome statistics (e.g. OR and HR, adjusted and unadjusted). Given the above, pooling of data for each type of test was deemed to be inappropriate. As such, the summary results below are based on non-statistical assessment of trends across studies.

The data show variability in prognostic effect sizes across the studies. In most assessments of association between a PFT designation of 'aspirin resistance' and clinical events, there are more studies with effect estimates above 1 (i.e. the risk of adverse clinical outcome in a group of patients designated 'aspirin resistant' is greater than that in a group designated 'aspirin sensitive'), but this was not uniform.

Many of the included studies contain very small numbers of patients and outcome events. This can lead to extreme prognostic effect estimates that arise merely by chance; however, the uncertainty about the estimates will be reflected by extremely wide CIs. Studies with extremely wide CIs covering values well above and below the null effect (e.g. intervals spanning ORs or HRs from close to zero to over 20) are essentially providing very little, if any, useful information. Therefore, caution should be applied when focusing on the estimates from such studies, and rather the focus should be on the wide CIs that reflect the large uncertainty.

Overall, there is a possible trend suggestive of more clinical events occurring in those groups of patients designated 'aspirin resistant', with some results in some studies showing statistical significance; this is the case across the majority of tests (LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement), to a lesser extent for TEG, and with data for WBA not allowing many conclusions to be drawn. This trend is also fairly consistent across some outcomes (i.e. death, MACEs and ischaemic thrombotic events) irrespective of test, though the direction of effect is not always consistent for different thresholds applied to the data from the same study. There are very limited data on bleeding events and thus no inference could be drawn.

The results suggest that PFTs (specifically LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement and TEG) may have some prognostic value as they are fairly consistently associated with elevated risk of cardiovascular events (MACEs or death). However, as meta-analysis was not possible, no firm quantitative conclusions can be drawn as to their prognostic value. Given that the effect sizes for an association with clinical events are relatively small and highly uncertain, a determination of the diagnostic utility of PFTs (for an individual, determining if they are at higher risk of a clinical event) was not possible in this report.

Dual-therapy studies

The tests identified for assessing platelet function in patients on dual therapy (aspirin plus a second antiplatelet agent at the time of the PFT) are (i) LTA, (ii) VerifyNow® Aspirin, (iii) measurement of urinary or serum/plasma 11-dehydro-TxB_2 concentrations, (iv) PFA-100®, (v) WBA, (vi) TEG and (vii) other miscellaneous tests (see *Chapter 5*, *Dual therapy*). The original intention was to report and analyse these studies in a similar way to the studies in patients receiving monotherapy with aspirin. As a result of the complex nature of the searches and study selection process, and also issues around reporting, studies on dual-therapy patients were included and data extraction undertaken in parallel with that for monotherapy studies. As it remains unclear whether 'aspirin resistance' is a distinct biological entity, with specific underlying mechanisms, or signals a more general platelet hyperactivity state in which aspirin is simply insufficient to inhibit platelet responses on its own,[14,44,74] the interplay between aspirin and a second antiplatelet agent in terms of platelet inhibition is an area of intense research. While clinical trials have demonstrated that the addition of a second antiplatelet agent results in more pronounced platelet inhibition, and consequently reduced risk of MACEs and increased risk of bleeding,[5,22] it remains unknown whether or not poor platelet response to one agent is linked to poor response to the other. For example, a number of studies have shown that 'aspirin-resistant' patients had normal responses to clopidogrel;[195,282,283] conversely, a number of studies have reported concomitant resistance to both aspirin and clopidogrel.[98,142,284] Given the high variability and the limited evidence of prognostic utility found in patient cohorts taking aspirin alone, it was decided not to analyse the results in populations exposed to dual antiplatelet therapy, as this introduced an extra unpredictable variable. The data on 'aspirin resistance' (but not 'clopidogrel resistance') have, however, been extracted from the included studies, and are available for analysis (see *Appendix 4*).

Strengths and limitations of available evidence and the prognostic utility review

Considerations on the volume of evidence identified

Within the limited parameters of the review, it became clear that there was an underestimate of the number of studies available based on the initial scoping exercise. It had been assumed that any new studies identified would have been subsequent to the previous systematic reviews; however,

i. Not all the studies had been published since the previous systematic reviews, and thus the previous systematic reviews were not sufficiently comprehensive (see *Chapter 5*, *Systematic reviews*).
ii. As a more thorough approach to identifying the evidence was undertaken, this revealed a surprisingly large number of studies which scoping could not easily predict. This is exemplified by the large number of hard-copy articles which were retrieved in order to make selection judgements. This was often driven by the fact that the nature of the studies did not easily convey that relevant information for this report was available.
iii. It became clear that the nature of the studies, in terms of both the populations and the interventions, had also altered. Thus, more patients with acute rather than stable disease were included, particularly patients with ACS, acute stroke and patients undergoing PCIs.

The nature of the included populations also drove a change in the nature of the interventions, with many of the later studies including populations treated with aspirin plus at least one other antiplatelet agent.

A stepwise approach to analysis of the included studies was planned and this aided management of the large number of included studies.

Considerations on the reporting of available evidence

The availability of a larger-than-expected volume of evidence has already been discussed above, as has the unrepresentativeness of most existing systematic reviews. A further salient point is the amount of unreported evidence relevant to this report. One-third of the articles meeting the inclusion criteria for the prognostic/diagnostic review did not report the association between PFT results and subsequent clinical outcomes, despite both being measured in the study being reported. Although reporting of this association might not have been within the aims of these studies and was thus, understandably, not reported as a priority, it suggests that a large number of data were not accessible to this review. It was beyond the scope of this project to ascertain the availability of these data for analysis. Lack of reporting may also relate to results not being reported for all thresholds for a designation of 'aspirin resistance', and/or time points for outcome measurement, changes in antiplatelet treatment during the course of a study and items relevant to quality assessment (see *Monotherapy*).

Considerations on the analysis

Tests are measured on a continuous scale for each patient. However, the studies identified by our review focused predominantly on comparing test-positive ('aspirin-resistant') and test-negative ('aspirin-sensitive') groups, with 'resistant' and 'sensitive' groups defined by dichotomising the continuous test by a chosen threshold value. This was not surprising, and indeed the data extraction and meta-analysis strategy was planned to synthesise results for each threshold reported where possible. However, the chosen threshold value was often highly variable from study to study, and this was a major reason why meta-analysis was not deemed sensible. Some studies presented results for three or four categories (e.g. based on tertiles or quartiles). It is now recognised that it is better to analyse continuous variables on a continuous scale. Dichotomisation[285]/categorisation reduces power to detect genuine prognostic factors, and misses the opportunity to examine non-linear trends and the underlying prognostic association across the entire range of the factor's values. For meta-analysis, availability of individual patient data (IPD) would help synthesise linear and non-linear trends across multiple studies of the same factor.[286,287] Though the collection, cleaning and synthesis of IPD can be time-consuming and expensive,[288] it eases many problems with meta-analysis and avoids the complexity of extracting and dealing with multiple, variable and often selectively reported thresholds from published reports. However, an IPD analysis in the context of the current report would have required the consistent within- and between-study collection of all possible patient, test and outcome effect modifiers and a substantial proportion of study authors to make these data available. This was beyond the scope of this report and would likely be hampered by a number of factors, as outlined in the research recommendations (see *Recommendations for future research*).

Thus, pooling could only be considered for dichotomous data for each test. An array of data extraction and validated analysis methods allowed us to directly and indirectly obtain effect sizes and CIs from the included studies (see *Chapter 4*, *Prognostic ability: unadjusted and adjusted odds ratios and hazard ratios*). This led to substantially more information being available than would otherwise have been the case. Sometimes only rounded percentages of events were reported in each group (rather than exact numbers) and so only approximate numbers were obtainable.

However, as a result of poor or incomplete reporting, many studies did not allow suitable results to be extracted or calculated. In addition, even when the same types of effect sizes could be obtained from multiple studies of the same test, there was a vast amount of clinical and methodological heterogeneity across studies in important factors, as outlined above (see *Monotherapy*).

It was therefore decided that pooled results would be difficult to interpret meaningfully. The extracted results were therefore summarised on forest plots (but without pooled results). These plots provide the effect estimate and its CI for each study, alongside key clinical and methodological information such as the patient group, outcome, sample size, threshold level and agonist. The absence of the ability to pool studies meant that examinations of publication bias (e.g. funnel plots) were also not possible, which was unfortunate as publication bias is a known issue in prognosis research.[289–292]

Consideration on the usefulness of prognostic factors

Prognostic factors are defined as measurable characteristics associated with the risk of a subsequent outcome in people with a given disease or health condition. A recent series on prognosis research[293–296] discusses how a single prognostic factor rarely predicts individual outcome risk accurately, and usually does not suitably discriminate between high-risk and low-risk individuals, as in this report. This is why prognostic models are developed, as they utilise multiple prognostic factors in combination to improve individual risk prediction accuracy and to better discriminate the underlying risk across individuals. No prognostic models were identified that aimed to utilise multiple tests with multiple prognostic factors for the purpose of predicting individual outcome risk in patients on aspirin monotherapy for prevention of cardiovascular events.

It should be noted that prognostic factors do have a broad array of potential uses in both clinical practice and health research.[293–296] For instance, they help to define disease at diagnosis; they aid the design and analysis of trials; they are confounders to consider in observational studies and unbalanced trials; and they are the building blocks of risk prediction models. The designation of 'aspirin resistance' based on a PFT is a potential prognostic factor, but it should ideally be considered in conjunction with any other factors identified as prognostic of future adverse clinical outcomes. Thus, even if there was certainty around the prognostic utility of PTFs, there is a need to ascertain if any other factors have prognostic utility and, if so, ideally a prognostic model should be developed and validated to aid treatment management.

Summary of the economic evaluation

Currently, there is no existing economic evidence on the cost or cost-effectiveness of platelet function testing for 'aspirin resistance', which might seem surprising considering the amount of research identified by the systematic review of prognostic/diagnostic utility, the positive findings of many existing systematic reviews of prognostic utility of PFTs in this area and the degree of debate around this topic. This report presents the first model to attempt to estimate the cost-effectiveness of a 'test and change treatment' strategy using platelet function testing to define an at-risk population. The model is highly speculative owing to the large degree of heterogeneity and uncertainty around the prognostic utility of PFTs, and it contains numerous assumptions. This has been addressed, where possible, by the deterministic sensitivity analysis and also by taking into account the uncertainty around many of the model parameter values. In addition, further analyses have been presented to show scenarios where platelet function testing for 'aspirin resistance' and a change in treatment would not be cost-effective. The model structure may also be viewed as somewhat simplistic, with no recurrence of clinical events and no increase in the risk of events over time, but as the model is speculative, with few data to populate it, there would be little value in making the model unnecessarily complex at this stage.

Assuming that a PFT can accurately identify patients at higher risk of adverse clinical outcomes while receiving aspirin therapy as the sole antiplatelet agent, and patients changed to an effective treatment, then a 'test and change treatment' option is very likely to be cost-effective. Conversely, if a PFT cannot identify these patients, and a treatment change is not effective in reducing adverse clinical outcome (MACE) risk, then a 'test and change treatment' strategy is not cost-effective. The parameters with the greatest impact on model results are the proportion of patients who are correctly identified as having high risk of clinical outcome, the effectiveness of a change in treatment if designated 'aspirin resistant', the cost of a test and the cost of a change in treatment. The accuracy of testing, the additional risk of an adverse outcome associated with a designation of 'aspirin resistance' and the effectiveness of a change in therapy are the most uncertain parameters. The model requires more robust data on all of these aspects.

Recommendations for future research

The heterogeneity and methodological problems identified in this review are similar to other attempted meta-analyses of prognostic factor studies. Attempting to conduct and draw inferences from systematic reviews of prognostic factor studies is difficult.[293] Primary prognostic factor studies are often poorly designed, inappropriately analysed and poorly/selectively reported.[289–292,297–304] This leads to confusion about whether or not factors are genuinely prognostic, with the play of chance and selective reporting typically leading to overoptimism in the prognostic effect sizes seen in the literature.

Primary studies evaluating the prognostic ability of tests should focus on standardising how the tests are measured and conducting large, protocol-driven studies with statistical analysis plans that aim to examine prognostic and predictive ability. Guidelines for those planning and undertaking a prognostic factor study have been suggested and should be used, to ensure higher standards of study quality, design and analysis than are currently observed.[305,306] This is important in the current context as many studies included in the prognostic utility review had other primary aims (e.g. effectiveness of an intervention).

A prospective rather than retrospective design is preferable as it enables clear inclusion criteria, more complete baseline and follow-up data, and greater standardisation of diagnostic and therapeutic procedures, as well as ensuring that the primary factors and outcomes can be specified in advance, reducing the potential for data dredging and thus type I errors and selective reporting. This is especially important in larger studies aiming to replicate earlier exploratory prognostic factor findings, and these should incorporate a suitable sample size calculation to ensure adequate power to detect an important prognostic effect, if one exists. Statistical analysis methods can be improved by analysing continuous factors on their continuous scale, thereby avoiding the use of arbitrary threshold levels to categorise them; by considering non-linear relationships; and by including multivariable analyses that assess a factor's prognostic value over existing prognostic factors.[293]

Future research should ideally concentrate on developing and validating prognostic models that utilise multiple prognostic factors in combination. For an individual with a given state of health (start point), a prognostic model converts the combination of predictor values to an estimate of the risk of experiencing a specific end point within a specific time period. Ideally, this produces an estimate of the absolute risk (absolute probability) of experiencing the end point. This is the information that clinicians require to make decisions, rather than reliance on the result of a single PFT. One option is to use IPD from high-quality, prospective, primary studies that use very similar clinical populations and measure similar tests, patient characteristics (prognostic factors) and outcomes.[295] Having IPD from multiple studies offers a natural opportunity to increase sample size and essentially develop a prognostic model within a meta-analysis framework.[307] Variation in model accuracy across studies, and its causes, can be explored. Additionally, such collaborative efforts encourage consensus towards a single, well-developed and validated prognostic model, rather than a number of competing and non-validated models for the same clinical problem, championed by each group separately.

However, in the current context, an IPD meta-analysis would be hampered by substantial heterogeneity across studies, even if only a single PFT at a time was considered in a well-defined population. In particular, heterogeneity relates to test thresholds used, variability in test methods, timing of test and length of follow-up, and range and definition of clinical events. A large number of variables would likely need to be considered (e.g. smoking status, age, sex, prior events, disease severity, diabetes, mean platelet volume, etc.), even allowing for the fact that not all will be found to have a significant effect. Given that a minimum of 10 events per variable is considered necessary in a prognostic model, the frequently low event rates in studies limit the number of variables that can be assessed. An IPD analysis may also be biased, depending on which study authors make their data available and the different methodological quality of the studies.

Given the above, using IPD from existing studies could render a useful prognostic model improbable to build. Therefore, one or more new prospective cohort studies may be a more feasible option. A primary study could incorporate the following elements, the majority of which have not been appropriately considered in existing studies:

- several tests performed in the same individuals (at present there are very few studies looking at more than one or two tests)
- standardisation of laboratory methods
- tests performed in duplicate to assess variability
- repeat tests to assess variability over time
- sufficiently large sample size to allow for sufficient events in both resistant and sensitive groups
- sufficiently long follow-up for relevant clinical outcomes to occur
- use of standardised criteria for individual outcomes, and also individual reporting of all outcomes contributing to composite outcome measures
- rigorous assessment of adherence
- robust methodological quality
- analyses could be undertaken for different test thresholds.

The above should be applied to one or more well-described cardiovascular/cerebrovascular population(s) and should also consider current treatment guidelines with regard to antiplatelet therapy for the given population.

The aim of a primary study would be to (i) identify what tests (variables) have a prognostic association with future outcomes, both on their own (unadjusted) and independent of other prognostic factors (adjusted); and (ii) develop a prognostic model that utilises the identified prognostic tests and variables in combination, in order to predict absolute risk of adverse outcomes for future individuals.

Before initiating such a study, a group of clinical and methodological leaders in the field should meet and agree criteria such as the tests to be measured, the relevant clinical populations and timing of test measurement, how the tests are measured, and what outcomes are relevant and how these are measured.

If more than one new cohort study is to be undertaken on a similar population, ideally this should be done in collaboration, ensuring similar protocols, methodology and factors/tests to be recorded, with agreement to pool IPD once each individual study is completed. This would ensure reduced heterogeneity across studies and the opportunity to then simultaneously develop and validate a model.

Once these issues have been addressed it may be possible to undertake a ‘test–treat trial’ using a prognostic model to tailor antiplatelet therapy to individuals.

Chapter 8 Conclusions

The current report has failed to demonstrate a convincing association between 'aspirin resistance', as defined by a PFT, and clinical outcome, on any test and in any outcome, despite the existence of a vast number of studies which have sought to clarify this association. The issues surrounding potential inaccessibility of relevant data and the heterogeneity across all of the study parameters have been discussed. The implications of a designation of 'aspirin resistance' based on a PFT remain uncertain and, thus, so does the question of how best to define 'aspirin resistance'. Until a definitive study has been undertaken to answer this question, which must include some measure of adherence to therapy, platelet function testing has no demonstrable clinical utility.

Although evidence indicates that some tests may have some prognostic value, methodological and clinical heterogeneity of studies and different approaches to analyses create confusion and inconsistency in prognostic results, and prevented a quantitative summary of their prognostic effect. Large, protocol-driven and adequately powered primary studies are needed, using standardised and agreed methods of measurements to evaluate the prognostic ability of each test in the same population(s). For PFTs to inform individual risk prediction, and thus be useful for clinical decision-making, it is likely that they need to be considered in combination and alongside other prognostic factors, within a prognostic model.

Acknowledgements

The authors thank the following:

Simon Stevens for his invaluable administrative support, excellent organisational skills and heroic efforts to source articles.

Jo Hine for additional administrative support.

Steve Watson, Paul Harrison and Gregory Y H Lip for clinical and platelet function testing guidance.

Pelham Barton for economic modelling guidance.

All the people who kindly gave their time to help translate articles.

Contribution of authors

Janine Dretzke wrote and edited sections of the report and undertook study selection, data extraction and quality assessment for the prognostic review.

Richard D Riley devised, led and executed the statistical analysis, extracted statistical data for the prognostic review and wrote sections of the report.

Marie Lordkipanidzé provided detailed knowledge of the PFTs, their utilisation and interpretation of their results, undertook study selection for the prognostic review and wrote the background section of the report.

Susan Jowett led the economic section of the report, contributed to all parts of the economic review and development of the economic model and associated analysis, and wrote sections of the report.

Jennifer O' Donnell undertook study selection, data extraction and quality assessment for the prognostic review, and contributed to several sections of the report.

Joie Ensor contributed to the plan for statistical analysis and interpretation of the data, extracted statistical data for the prognostic review, managed the flow of statistical evidence and contributed to several sections of the report.

Eoin Moloney contributed to all parts of the economic review and development of the economic model and associated analysis, and wrote sections of the report.

Malcolm Price contributed to the plan for statistical analysis and interpretation of the data and extracted statistical data for the prognostic review.

Smriti Raichand contributed to the development of the protocol and undertook study selection.

James Hodgkinson undertook data extraction and an appraisal of existing systematic reviews.

Susan Bayliss contributed to deriving the search strategies and ran the searches in electronic databases.

David Fitzmaurice contributed to all parts of the project, undertook study selection, provided clinical insight, wrote sections of the report and takes responsibility for overall content.

David Moore led the review section of the report, contributed to all parts of the project, undertook study selection, compiled the report, and wrote and edited sections of the report.

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Dretzke J, Riley R, Lordkipanidzé M, Jowett S, O'Donnell J, Ensor J, *et al.* Protocol for a systematic review of the diagnostic and prognostic utility of tests currently available for the detection of aspirin resistance in patients with established cardiovascular or cerebrovascular disease. *Syst Rev* 2013;**2**:16.

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Appendix 1 Search strategies: prognostic/diagnostic utility review

Database: MEDLINE (Ovid) (1946 to April week 3, 2012)

1. ((ASA or aspirin or acetylsalicylic or anti platelet or antiplatelet or anti-platelet) adj2 (respons$ or non-respons$ or respond$ or non-respond$ or resistance or resist$)).mp
2. (platelet adj (response or respond$ or reactivity)).mp.
3. 1 or 2
4. exp Aspirin/
5. exp Drug Resistance/
6. 4 and 5
7. 3 or 6
8. (platelet function adj (analys$ or analyz$)).mp.
9. (platelet function adj (assay$ or test$)).mp.
10. Platelet Function Tests/
11. PFA-100.mp.
12. PlateletWorks.mp.
13. Platelet Mapping.mp.
14. Impact Cone.mp.
15. platelet analyser$.mp.
16. platelet analyzer$.mp.
17. multiplate.mp.
18. aggregometry.mp.
19. LTA.mp.
20. AA-induced LTA.mp.
21. lumiaggregometry.mp.
22. WBA.mp.
23. ULTEGRA assay.mp.
24. Impact-R.mp.
25. TRAP-6.mp.
26. TEG.mp.
27. s-TEG.mp.
28. thromboelastometry.mp.
29. ROTEM.mp.
30. VerifyNow.mp.
31. Verify-Now.mp.
32. VN-RPFA.mp.
33. VASP.mp.
34. VASP-P.mp.
35. platelet reactivity index.mp.
36. vasodilator-stimulated phosphoprotein phosphorylation assay$.mp.
37. T-Guide.tw.
38. T Guide.ti,ab.
39. xylum clot signature analyser.mp.
40. xylum clot signature analyzer.mp.
41. ASA test$.mp.
42. ASA assay$.mp.
43. AA-induced LTA.mp.
44. exp Platelet Count/ or platelet counting.mp.

45. thrombelastography.mp. or Thrombelastography/
46. thrombotic status analyser$.mp.
47. thrombotic status analyzer$.mp.
48. or/8-47
49. exp Cardiovascular Diseases)
50. exp Cerebrovascular Disorders/
51. exp Diabetes Mellitus/
52. or/49-51
53. 48 and 52
54. (predict$ or prognos$).mp.
55. 48 and 54
56. 7 or 53
57. 7 or 55
58. 56 or 57
59. exp animals/ not humans/
60. 58 not 59

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations (25 April 2012)

1. ((ASA or aspirin or acetylsalicylic or anti platelet or antiplatelet or anti-platelet) adj2 (respons$ or non-respons$ or respond$ or non-respond$ or resistance or resist$)).mp.
2. (platelet adj (response or respond$ or reactivity)).mp.
3. 1 or 2
4. (platelet function adj (analys$ or analyz$)).mp.
5. (platelet function adj (assay$ or test$)).mp.
6. PFA-100.mp.
7. PlateletWorks.mp.
8. Platelet Mapping.mp.
9. Impact Cone.mp.
10. platelet analyser$.mp.
11. platelet analyzer$.mp.
12. multiplate.mp.
13. aggregometry.mp.
14. LTA.mp.
15. AA-induced LTA.mp.
16. lumiaggregometry.mp.
17. WBA.mp.
18. ULTEGRA assay.mp.
19. Impact-R.mp.
20. TRAP-6.mp.
21. TEG.mp.
22. s-TEG.mp.
23. thromboelastometry.mp.
24. ROTEM.mp.
25. VerifyNow.mp.
26. Verify-Now.mp.
27. VN-RPFA.mp.
28. VASP.mp.
29. VASP-P.mp.
30. platelet reactivity index.mp.
31. vasodilator-stimulated phosphoprotein phosphorylation assay$.mp.

32. T-Guide.tw.
33. T Guide.ti,ab.
34. xylum clot signature analyser.mp.
35. xylum clot signature analyzer.mp.
36. ASA test$.mp.
37. ASA assay$.mp.
38. AA-induced LTA.mp.
39. exp Platelet Count/ or platelet counting.mp.
40. thrombelastography.mp. or Thrombelastography/
41. thrombotic status analyser$.mp.
42. thrombotic status analyzer$.mp.
43. or/4-42
44. (cardiovascular or cerebrovascular or diabetes).mp.
45. 43 and 44
46. (predict$ or prognos$).mp.
47. 43 and 46
48. 3 or 45
49. 3 or 47
50. 48 or 49

Database: EMBASE (Ovid) (1980 to week 16, 2012)

1. ((ASA or aspirin or acetylsalicylic or anti platelet or antiplatelet or anti-platelet) adj2 (respons$ or non-respons$ or respond$ or non-respond$ or resistance or resist$)).mp
2. (platelet adj (response or respond$ or reactivity)).mp.
3. 1 or 2
4. exp acetylsalicylic acid/
5. exp drug resistance/
6. 4 and 5
7. 3 or 6
8. (platelet function adj (analys$ or analyz$)).mp.
9. (platelet function adj (assay$ or test$)).mp.
10. PFA-100.mp.
11. PlateletWorks.mp.
12. Platelet Mapping.mp.
13. Impact Cone.mp.
14. platelet analyser$.mp.
15. platelet analyzer$.mp.
16. multiplate.mp.
17. aggregometry.mp.
18. LTA.mp.
19. AA-induced LTA.mp.
20. lumiaggregometry.mp.
21. WBA.mp.
22. ULTEGRA assay.mp.
23. Impact-R.mp.
24. TRAP-6.mp.
25. TEG.mp.
26. s-TEG.mp.
27. thromboelastometry.mp.
28. ROTEM.mp.
29. VerifyNow.mp.

30. Verify-Now.mp.
31. VN-RPFA.mp.
32. VASP.mp.
33. VASP-P.mp.
34. platelet reactivity index.mp.
35. vasodilator-stimulated phosphoprotein phosphorylation assay$.mp.
36. T Guide.mp.
37. T-Guide.mp.
38. xylum clot signature analy$.mp.
39. ASA tests$.mp.
40. ASA assay$.mp.
41. AA-induced LTA.mp.
42. platelet counting.mp.
43. thrombelastography.mp. or exp thromboelastography/
44. thrombotic status analy$.mp.
45. or/8-44
46. exp cardiovascular disease/
47. exp cerebrovascular disease/
48. exp diabetes mellitus/
49. or/46-48
50. 45 and 49
51. (predict$ or prognos$).mp.
52. 45 and 51
53. 7 or 50
54. 7 or 52
55. 53 or 54
56. exp animal/ not human/
57. 55 not 56

Database: The Cochrane Library (Wiley) (Cochrane Central Register of Controlled Trials 2012, issue 4 of 12)

#1 (ASA or aspirin or acetylsalicylic or anti next platelet or antiplatelet) near/2 (respon* or non next respon* or resist*)

#2 (platelet) near/1 (response or respond* or reactivity)

#3 (#1 OR #2)

#4 MeSH descriptor Aspirin explode all trees

#5 MeSH descriptor Drug Resistance explode all trees

#6 (#4 AND #5)

#7 (#3 OR #6)

#8 (platelet function) near/1 (analys* or analyz*)

#9 (platelet function) near/1 (assay* or test*)

#10 PFA-100

#11 PlateletWorks

#12 Platelet next Mapping

#13 Cone

#14 platelet next analy*

#15 multiplate

#16 aggregometry

#17 LTA

#18 lumiaggregometry

#19 WBA

#20 ULTEGRA

#21 Impact-R

#22 TRAP-6

#23 TEG

#24 thromboelastometry

#25 ROTEM

#26 VerifyNow

#27 Verify-Now

#28 VN-RPFA

#29 VASP

#30 VASP-P

#31 platelet next reactivity next index

#32 vasodilator next stimulated next phosphoprotein

#33 T next Guide

#34 xylum next clot

#35 (ASA) next (test* or assay*)

#36 AA next induced

#37 platelet next counting

#38 thromboelastography

#39 thrombotic next status next analy*

#40 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)

#41 MeSH descriptor Cardiovascular Diseases explode all trees

#42 MeSH descriptor Cerebrovascular Disorders explode all trees

#43 MeSH descriptor Diabetes Mellitus explode all trees

#44 (#41 OR #42 OR #43)

#45 (#40 AND #44)

#46 predict* or prognos*

#47 (#40 AND #46)

#48 (#7 OR #45)

#49 (#7 OR #47)

#50 (#48 OR #49)

Conference proceedings searches

Database: Science Citation Index (Web of Knowledge) (searched 1 May 2012)

Title= (aspirin resistance)

Refined by: Web of Science Categories=(PERIPHERAL VASCULAR DISEASE OR CARDIAC CARDIOVASCULAR SYSTEMS) AND Document Type=(MEETING ABSTRACT)

Timespan=All Years. Databases=SCI-EXPANDED.

Lemmatization=On

Title=(platelet function test*)

Refined by: Web of Science Categories=(PERIPHERAL VASCULAR DISEASE OR CARDIAC CARDIOVASCULAR SYSTEMS) AND Document Type=(MEETING ABSTRACT)

Timespan=All Years. Databases=SCI-EXPANDED.

Database: Conference Proceedings Citation Index (Web of Knowledge) (searched 1 May 2012)

Title=(aspirin resistance)

Refined by: Web of Science Categories=(CARDIAC CARDIOVASCULAR SYSTEMS OR PERIPHERAL VASCULAR DISEASE) AND Document Type=(MEETING ABSTRACT OR PROCEEDINGS PAPER)

Timespan=All Years. Databases=CPCI-S.

Title=(platelet function test*)

Refined by: Web of Science Categories=(CARDIAC CARDIOVASCULAR SYSTEMS OR PERIPHERAL VASCULAR DISEASE) AND Document Type=(MEETING ABSTRACT OR PROCEEDINGS PAPER)

Timespan=All Years. Databases=CPCI-S.

Appendix 2 Search strategies for economic studies

Database: MEDLINE (Ovid) (1946 to April week 4, 2012)

1. ((ASA or aspirin or acetylsalicylic or anti platelet or antiplatelet or anti-platelet) adj2 (respons$ or non-respons$ or respond$ or non-respond$ or resistance or resist$)).mp.
2. (platelet adj (response or respond$ or reactivity)).mp.
3. 1 or 2
4. exp Aspirin/
5. exp Drug Resistance/
6. 4 and 5
7. 3 or 6
8. (platelet function adj (analys$ or analyz$)).mp.
9. (platelet function adj (assay$ or test$)).mp.
10. Platelet Function Tests/
11. PFA-100.mp.
12. PlateletWorks.mp.
13. Platelet Mapping.mp.
14. Impact Cone.mp.
15. platelet analyser$.mp.
16. platelet analyzer$.mp.
17. multiplate.mp.
18. aggregometry.mp.
19. LTA.mp.
20. AA-induced LTA.mp.
21. lumiaggregometry.mp.
22. WBA.mp.
23. ULTEGRA assay.mp.
24. Impact-R.mp.
25. TRAP-6.mp.
26. TEG.mp.
27. s-TEG.mp.
28. thromboelastometry.mp.
29. ROTEM.mp.
30. VerifyNow.mp.
31. Verify-Now.mp.
32. VN-RPFA.mp.
33. VASP.mp.
34. VASP-P.mp.
35. platelet reactivity index.mp.
36. vasodilator-stimulated phosphoprotein phosphorylation assay$.mp.
37. T-Guide.tw.
38. T Guide.ti,ab.
39. xylum clot signature analyser.mp.
40. xylum clot signature analyzer.mp.
41. ASA test$.mp.
42. ASA assay$.mp.
43. AA-induced LTA.mp.
44. exp Platelet Count/ or platelet counting.mp.

45. thrombelastography.mp. or Thrombelastography/
46. thrombotic status analyser$.mp.
47. thrombotic status analyzer$.mp.
48. or/8-47
49. exp Cardiovascular Diseases/
50. exp Cerebrovascular Disorders/
51. exp Diabetes Mellitus/
52. or/49-51
53. 48 and 52
54. (predict$ or prognos$).mp.
55. 48 and 54
56. 7 or 53
57. 7 or 55
58. 56 or 57
59. economics/
60. exp "costs and cost analysis"/
61. cost of illness/
62. exp health care costs/
63. economic value of life/
64. exp economics medical/
65. exp economics hospital/
66. economics pharmaceutical/
67. exp "fees and charges"/
68. (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
69. (expenditure$ not energy).tw.
70. (value adj1 money).tw.
71. budget$.tw.
72. decision support techniques/
73. markov.mp.
74. exp models economic/
75. decision analysis.mp.
76. cost benefit analysis/
77. or/59-76
78. 58 and 77

Database: EMBASE (Ovid) (1980 to week 17, 2012)

1. ((ASA or aspirin or acetylsalicylic or anti platelet or antiplatelet or anti-platelet) adj2 (respons$ or non-respons$ or respond$ or non-respond$ or resistance or resist$)).mp.
2. (platelet adj (response or respond$ or reactivity)).mp.
3. 1 or 2
4. exp acetylsalicylic acid/
5. exp drug resistance/
6. 4 and 5
7. 3 or 6
8. (platelet function adj (analys$ or analyz$)).mp.
9. (platelet function adj (assay$ or test$)).mp.
10. PFA-100.mp.
11. PlateletWorks.mp.
12. Platelet Mapping.mp.
13. Impact Cone.mp.

14. platelet analyser$.mp.
15. platelet analyzer$.mp.
16. multiplate.mp.
17. aggregometry.mp.
18. LTA.mp.
19. AA-induced LTA.mp.
20. lumiaggregometry.mp.
21. WBA.mp.
22. ULTEGRA assay.mp.
23. Impact-R.mp.
24. TRAP-6.mp.
25. TEG.mp.
26. s-TEG.mp.
27. thromboelastometry.mp.
28. ROTEM.mp.
29. VerifyNow.mp.
30. Verify-Now.mp.
31. VN-RPFA.mp.
32. VASP.mp.
33. VASP-P.mp.
34. platelet reactivity index.mp.
35. vasodilator-stimulated phosphoprotein phosphorylation assay$.mp.
36. T Guide.mp.
37. T Guide.mp.
38. xylum clot signature analy$.mp.
39. ASA tests$.mp.
40. ASA assay$.mp.
41. AA-induced LTA.mp.
42. platelet counting.mp.
43. thrombelastography.mp. or exp thromboelastography/
44. thrombotic status analy$.mp.
45. or/8-44
46. exp cardiovascular disease/
47. exp cerebrovascular disease/
48. exp diabetes mellitus/
49. or/46-48
50. 45 and 49
51. (predict$ or prognos$).mp
52. 45 and 51
53. 7 or 50
54. 7 or 52
55. 53 or 54
56. cost benefit analysis/
57. cost effectiveness analysis/
58. cost minimization analysis/
59. cost utility analysis/
60. economic evaluation/
61. (cost or costs or costed or costly or costing).tw.
62. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
63. (technology adj assessment$).tw.
64. decision support.mp.
65. markov.mp.

66. exp statistical model/
67. decision analysis.mp.
68. exp "cost benefit analysis"/
69. or/56-68
70. 55 and 69

Database: The Cochrane Library (Wiley) (NHS Economic Evaluation Database) (2012, issue 2 of 4)

(Search date 4 May 2012.)

#1 (ASA or aspirin or acetylsalicylic or anti next platelet or antiplatelet) near/2 (respon* or non next respon* or resist*)

#2 (platelet) near/1 (response or respond* or reactivity)

#3 (#1 OR #2)

#4 MeSH descriptor Aspirin explode all trees

#5 MeSH descriptor Drug Resistance explode all trees

#6 (#4 AND #5)

#7 (#3 OR #6)

#8 (platelet function) near/1 (analys* or analyz*)

#9 (platelet function) near/1 (assay* or test*)

#10 PFA-100

#11 PlateletWorks

#12 Platelet next Mapping

#13 Cone

#14 platelet next analy*

#15 multiplate

#16 aggregometry

#17 LTA

#18 lumiaggregometry

#19 WBA

#20 ULTEGRA

#21 Impact-R

#22 TRAP-6

#23 TEG

#24 thromboelastometry

#25 ROTEM

#26 VerifyNow

#27 Verify-Now

#28 VN-RPFA

#29 VASP

#30 VASP-P

#31 platelet next reactivity next index

#32 vasodilator next stimulated next phosphoprotein

#33 T next Guide

#34 xylum next clot

#35 (ASA) next (test* or assay*)

#36 AA next induced

#37 platelet next counting

#38 thromboelastography

#39 thrombotic next status next analy*

#40 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)

#41 MeSH descriptor Cardiovascular Diseases explode all trees

#42 MeSH descriptor Cerebrovascular Disorders explode all trees

#43 MeSH descriptor Diabetes Mellitus explode all trees

#44 (#41 OR #42 OR #43)

#45 (#40 AND #44)

#46 predict* or prognos*

#47 (#40 AND #46)

#48 (#7 OR #45)

#49 (#7 OR #47)

#50 (#48 OR #49)

Appendix 3 Sensitivities and specificities

As outlined in *Chapter 4*, *Diagnostic/predictive accuracy*, there are limitations with regard to assessment of the diagnostic utility of PFTs in the context of prediction of future adverse clinical outcomes in aspirin-treated patients.

Sensitivities and specificities were rarely reported by studies included in this report. Where data were available to calculate these metrics, they were extracted. In both cases the reference standard for calculations was the occurrence, or not, of a named clinical outcome. The presence of these data is mentioned where relevant in the main results section of this report (see *Chapter 5*). As studies frequently reported more than one clinical outcome, there was the possibility of using multiple reference standards. In such cases, sensitivities and specificities are presented for each outcome. It should be noted that the occurrence of a clinical outcome is not necessarily indicative of a poor response to aspirin therapy, as the outcome might also occur by chance or as a result of other factors, such as poor adherence to therapy.

This appendix reports a speculative analysis of diagnostic utility for each group of PFTs in patients receiving aspirin as a monotherapy at the time of platelet function testing for each clinical outcome. Brief methods are outlined below prior to presentation of the results.

Methods

The diagnostic/predictive accuracy of each test relates to the absolute scale and summarises its ability to accurately classify which patients go on to experience clinically important outcomes. For test results classed as 'positive' or 'negative' (or 'high' or 'low') and linked to a binary outcome at a particular time, the data required to complete a 2 × 2 table were sought (*Table 84*).

When available, the 2 × 2 table allowed estimation of the sensitivity [a/(a + c)] and specificity [b/(b + d)] of the test, with CIs, and (for cohort studies) the prevalence of the outcome (a + c)/(b + d). Sensitivity is defined as the probability of correctly classifying those patients who ultimately experience an event as test positive, and specificity as the probability of correctly classifying those who do not go on to experience an event as test negative. If studies provided a 2 × 2 table with one or both groups having a zero cell, then a continuity correction of 0.5 was added to all cells in order to work out the variance and CI for sensitivity and specificity.[308] CIs were derived on the logit scale, and then transformed back to the original sensitivity and specificity scale.

Though most studies reported dichotomised test results (e.g. 'positive' vs. 'negative'), sometimes results were presented by three or more groups of test results (e.g. 'high', 'normal', 'low'). In this situation, to allow greater consistency across studies, the groupings were collapsed where possible to form a dichotomy again, and allow for the generation of tables that compared two groups (e.g. a table for 'high' vs. 'normal' or 'low', and one for 'high' or 'normal' vs. 'low').

TABLE 84 2 × 2 table to be extracted from each study for each binary outcome of interest

Test result	Number of patients with an event	Number of patients with no events
Test positive (aspirin resistant)	TP (a)	FP (b)
Test negative (aspirin sensitive)	FN (c)	TN (d)

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Owing to the clinical and methodological heterogeneity between studies, pooling of data was determined to be inappropriate even in subgroups of studies employing the same PFT. However, data are presented in this report in forest plots (without the summary estimate), along with some relevant study characteristics highlighting heterogeneity.

Results

In all sections below, given the uncertainty around the prognostic utility findings presented in the main body of this report, the sensitivities and specificities do not meaningfully contribute to the report.

Light transmission aggregometry: death

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Sensitivity (95% CI)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	0.33 (0.11 to 0.67)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	0.78 (0.42 to 0.94)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	1.00 (0.27 to 1.00)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	1.00 (0.27 to 1.00)

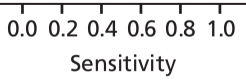

FIGURE 69 Light transmission aggregometry, monotherapy: death, sensitivity. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Specificity (95% CI)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	0.77 (0.67 to 0.84)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	0.26 (0.18 to 0.35)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	0.83 (0.78 to 0.87)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	0.74 (0.61 to 0.83)

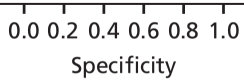

FIGURE 70 Light transmission aggregometry, monotherapy: death, specificity. AA, arachidonic acid.

Light transmission aggregometry: major adverse cardiac events

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Sensitivity (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	All vascular events including stroke	0.00 (0.00 to 0.67)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	AA (0.5 mg/ml)	78%		0.53 (0.29 to 0.76)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%		0.87 (0.59 to 0.97)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%		0.77 (0.48 to 0.92)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	20%	6 months	0.67 (0.45 to 0.83)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	20%	15 months	0.31 (0.12 to 0.59)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	40%	6 months	0.29 (0.13 to 0.51)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	40%	15 months	0.27 (0.16 to 0.42)

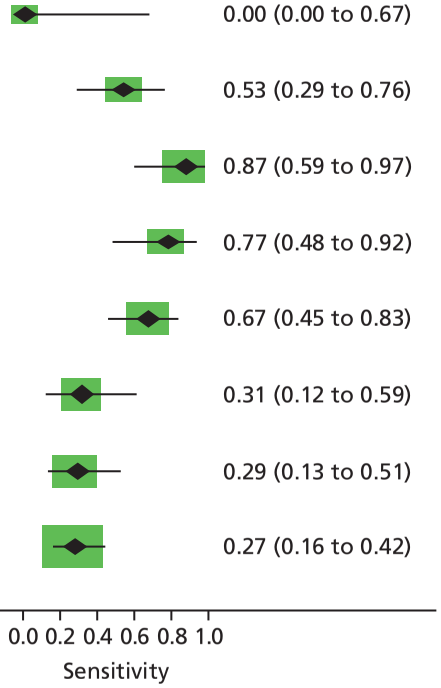

FIGURE 71 Light transmission aggregometry, monotherapy: MACEs, sensitivity. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Specificity (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	All vascular events including stroke	0.96 (0.85 to 0.99)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	AA (0.5 mg/mL)	78%		0.80 (0.71 to 0.87)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%		0.27 (0.19 to 0.37)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%		0.37 (0.23 to 0.52)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	20%	6 months	0.33 (0.20 to 0.51)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	20%	15 months	0.66 (0.50 to 0.79)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	40%	6 months	0.64 (0.46 to 0.78)
Spectre	2011[93]	Israel	54	PPCI/ACS	Mono before PCI, dual post PCI	AA (1.6 mM)	40%	15 months	0.84 (0.78 to 0.88)

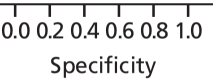

FIGURE 72 Light transmission aggregometry, monotherapy: MACEs, specificity. AA, arachidonic acid.

Light transmission aggregometry: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Sensitivity (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	Stroke	1.00 (0.19 to 1.00)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	MI	1.00 (0.11 to 1.00)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	MI	1.00 (0.11 to 1.00)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI (no PCI)	0.00 (0.00 to 0.81)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI with PCI	0.36 (0.14 to 0.66)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	Non-fatal stroke	1.00 (0.38 to 1.00)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	Non-fatal stroke	0.80 (0.31 to 0.97)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Stroke and/or TIA	0.25 (0.08 to 0.55)
Sørensen	1983[155]	Denmark	41	CVD/stroke	Mono	ADP (10 µM)	1 umol/l	Stroke or death	1.00 (0.19 to 1.00)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	UA	0.15 (0.04 to 0.45)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Any outcome	0.63 (0.28 to 0.87)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Peripheral arterial occlusions with revascularisation	0.00 (0.00 to 0.73)

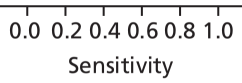

FIGURE 73 Light transmission aggregometry, monotherapy: ischaemic/thrombotic events, sensitivity. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Specificity (95% CI)
Kempfert	2009[113]	Germany	58	CAD	Mono post-op; 3 pre-op clopidogrel	AA (1 mM)	30%	Stroke	0.72 (0.59 to 0.82)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	MI	0.76 (0.67 to 0.83)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	MI	0.25 (0.18 to 0.35)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI (no PCI)	0.82 (0.77 to 0.86)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	MI with PCI	0.83 (0.78 to 0.87)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	40%	Non-fatal stroke	0.26 (0.19 to 0.36)
Cha	2008[121]	The Republic of Korea	107	CVD/stroke	Mono	ADP (10 µM)	61%	Non-fatal stroke	0.78 (0.69 to 0.85)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Stroke and/or TIA	0.82 (0.77 to 0.86)
Sørensen	1983[155]	Denmark	41	CVD/stroke	Mono	ADP (10 µM)	1 µmol/l	Stroke or death	0.72 (0.59 to 0.82)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	UA	0.82 (0.77 to 0.86)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Any outcome	0.64 (0.46 to 0.78)
Feher	2011[88]	Hungary	281	CVD/stroke	Mono	Not stated	Not stated	Peripheral arterial occlusions with revascularisation	0.82 (0.77 to 0.86)

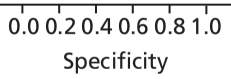

FIGURE 74 Light transmission aggregometry, monotherapy: ischaemic/thrombotic events, specificity. AA, arachidonic acid.

FIGURE 75 VerifyNow® Aspirin, monotherapy: death, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Ozben	2011[86]	Turkey	106	CVD/stroke	Mono	550	In-hospital mortality	0.71 (0.61 to 0.79)
Ozben	2011[86]	Turkey	106	CVD/stroke	Mono	550	2-year mortality	0.78 (0.66 to 0.86)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Death	0.82 (0.76 to 0.87)

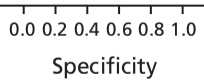

FIGURE 76 VerifyNow® Aspirin, monotherapy: death, specificity.

VerifyNow® Aspirin: major adverse cardiac events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550		0.10 (0.02 to 0.31)
Chen	2007[133]	China	464	CAD	Mono	550		0.53 (0.37 to 0.68)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up at 30 days	0.33 (0.13 to 0.62)
Chu	2010[105]	New Zealand	286	UA/ACS	Mono in 89%, dual 11%	550	Non-NSAID users	0.36 (0.14 to 0.66)
Chu	2010[105]	New Zealand	244	UA/ACS	Mono in 89%, dual 11%	550	Non-diabetics	0.33 (0.11 to 0.67)
Chu	2010[105]	New Zealand	269	UA/ACS	Mono in 89%, dual 11%	550	Non-smokers	0.25 (0.06 to 0.62)
Chu	2010[105]	New Zealand	19	UA/ACS	Mono in 89%, dual 11%	550	Toponin-T positive and medically managed	0.60 (0.22 to 0.88)
Chu	2010[105]	New Zealand	245	UA/ACS	Mono in 89%, dual 11%	550	Toponin-T negative and medically managed	0.17 (0.02 to 0.63)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up to 6 months	0.50 (0.31 to 0.69)

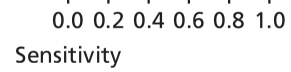

FIGURE 77 VerifyNow® Aspirin, monotherapy: MACEs, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550		0.81 (0.75 to 0.86)
Chen	2007[133]	China	464	CAD	Mono	550		0.75 (0.71 to 0.79)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up at 30 days	0.91 (0.88 to 0.94)
Chu	2010[105]	New Zealand	286	UA/ACS	Mono in 89%, dual 11%	550	Non-NSAID users	0.93 (0.89 to 0.96)
Chu	2010[105]	New Zealand	244	UA/ACS	Mono in 89%, dual 11%	550	Non-diabetics	0.93 (0.89 to 0.95)
Chu	2010[105]	New Zealand	269	UA/ACS	Mono in 89%, dual 11%	550	Non-smokers	0.92 (0.88 to 0.95)
Chu	2010[105]	New Zealand	19	UA/ACS	Mono in 89%, dual 11%	550	Toponin-T positive and medically managed	1.00 (0.63 to 1.00)
Chu	2010[105]	New Zealand	245	UA/ACS	Mono in 89%, dual 11%	550	Toponin-T negative and medically managed	0.90 (0.86 to 0.94)
Chu	2010[105]	New Zealand	312	UA/ACS	Mono in 89%, dual 11%	550	All: follow-up to 6 months	0.94 (0.90 to 0.96)

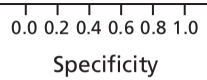

FIGURE 78 VerifyNow® Aspirin, monotherapy: MACEs, specificity.

VerifyNow® Aspirin: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Outcome	Sensitivity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion on days 1–3	0.11 (0.02 to 0.50)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion at 1 year	0.22 (0.10 to 0.41)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative MI	0.08 (0.01 to 0.39)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative stroke	0.00 (0.00 to 0.73)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Repear revascularisation	0.25 (0.03 to 0.76)

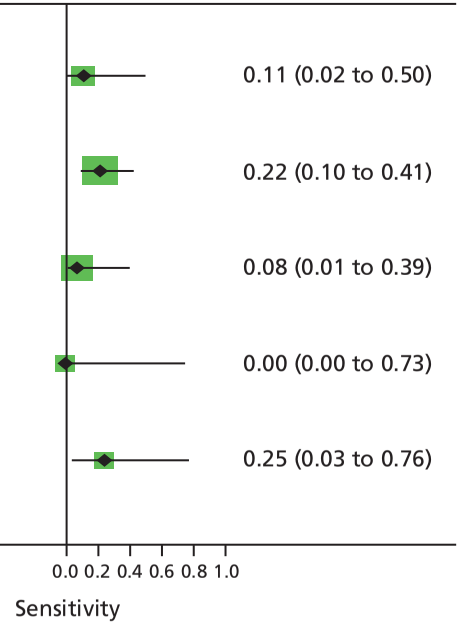

FIGURE 79 VerifyNow® Aspirin, monotherapy: ischaemic/thrombotic events, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Outcome	Specificity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion on days 1–3	0.82 (0.76 to 0.87)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Graft occlusion at 1 year	0.83 (0.77 to 0.88)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative MI	0.82 (0.76 to 0.86)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Postoperative stroke	0.82 (0.76 to 0.86)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Repeat revascularisation	0.82 (0.77 to 0.87)

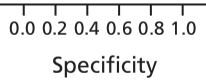

FIGURE 80 VerifyNow® Aspirin, monotherapy: ischaemic/thrombotic events, specificity.

VerifyNow® Aspirin: bleeding events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Re-exploration for bleeding	0.00 (0.00 to 0.81)

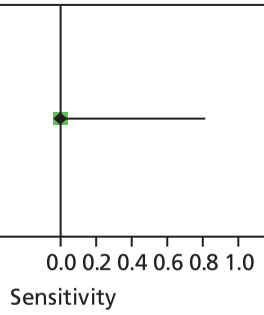

FIGURE 81 VerifyNow® Aspirin, monotherapy: bleeding events, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Kim	2011[92]	The Republic of Korea	220	CABG	Mono when test taken; ticlopidine post-op	550	Re-exploration for bleeding	0.82 (0.76 to 0.87)

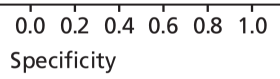

FIGURE 82 VerifyNow® Aspirin, monotherapy: bleeding events, specificity.

Thromboxane metabolite measurement: death

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Serum/plasma								
Frelinger	2009[76]	USA	682	CAD	Mono 68%, dual 32%	3.1 ng/ml	All-cause mortality	0.10 (0.03 to 0.28)
Frelinger	2009[76]	USA	660	CAD	Mono 68%, dual 32%	3.1 ng/ml	Cardiovascular mortality	0.29 (0.07 to 0.67)

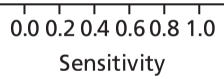

FIGURE 83 Thromboxane metabolite measurement, monotherapy: death, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Serum/plasma								
Frelinger	2009[76]	USA	682	CAD	Mono 68%, dual 32%	3.1 ng/ml	All-cause mortality	0.92 (0.90 to 0.94)
Frelinger	2009[76]	USA	660	CAD	Mono 68%, dual 32%	3.1 ng/ml	Cardiovascular mortality	0.92 (0.90 to 0.94)

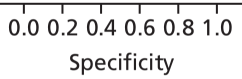

FIGURE 84 Thromboxane metabolite measurement, monotherapy: death, specificity.

Thromboxane metabolite measurement: major adverse cardiac events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Serum/plasma								
Cotter	2004[46]	Israel/USA	73	CAD	Mono	5 nmole/10^{11} platelets	Cardiovascular events	0.67 (0.33 to 0.89)
Frelinger	2009[76]	USA	555	CAD	Mono 68%, dual 32%	3.1 ng/ml		0.12 (0.07 to 0.19)
Urinary								
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (RAVE)	0.75 (0.38 to 0.94)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (MACE)	0.60 (0.38 to 0.79)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (MACE)	0.45 (0.25 to 0.66)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (RAVE)	0.75 (0.38 to 0.94)
Eskandarian	2011[202]	Iran	124	CAD	Mono	< 134, 134 – 298, > 298	High vs. intermediate or low	0.63 (0.47 to 0.76)
Eskandarian	2011[202]	Iran	124	CAD	Mono	< 134, 134 – 298, > 298	High or intermediate vs. low	0.70 (0.54 to 0.82)

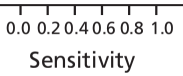

FIGURE 85 Thromboxane metabolite measurement, monotherapy: MACEs, sensitivity. RAVE, recurrent acute vascular event.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Serum/plasma								
Cotter	2004[46]	Israel/USA	73	CAD	Mono	5 nmole/10^{11} platelets	Cardiovascular events	0.77 (0.65 to 0.85)
Frelinger	2009[76]	USA	555	CAD	Mono 68%, dual 32%	3.1 ng/ml		0.93 (0.90 to 0.95)
Urinary								
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (RAVE)	0.34 (0.28 to 0.41)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First tertile vs. second and third tertile (MACE)	0.33 (0.27 to 0.40)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (RAVE)	0.68 (0.61 to 0.75)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	Tertiles	First and second tertile vs. third tertile (MACE)	0.69 (0.62 to 0.75)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High vs. intermediate or low	0.57 (0.46 to 0.67)
Eskandarian	2011[202]	Iran	124	CAD	Mono	<134, 134–298, >298	High or intermediate vs. low	0.37 (0.27 to 0.48)

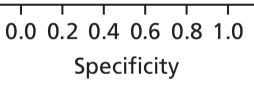

FIGURE 86 Thromboxane metabolite measurement, monotherapy: MACEs, specificity. RAVE, recurrent acute vascular event.

Thromboxane metabolite measurement: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Serum/plasma								
Cotter	2004[46]	Israel/USA	73	CAD	Mono	5 nmole/10^{11} platelets	Cardiovascular readmission	0.50 (0.28 to 0.72)

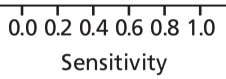

FIGURE 87 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Serum/plasma								
Cotter	2004[46]	Israel/USA	73	CAD	Mono	5 nmole/10^{11} platelets	Cardiovascular readmission	0.78 (0.65 to 0.87)

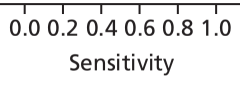

FIGURE 88 Thromboxane metabolite measurement, monotherapy: ischaemic/thrombotic events, specificity.

PFA-100®: death

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Sensitivity (95% CI)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	1.00 (0.19 to 1.00)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	0.38 (0.13 to 0.72)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186 s	0.43 (0.14 to 0.77)
Sambola	2004[145]	Spain	100	CAD	Mono	CEPI	193 s	1.00 (0.38 to 1.00)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	0.22 (0.09 to 0.43)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	0.22 (0.09 to 0.43)

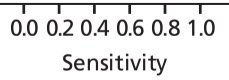

FIGURE 89 PFA-100®, monotherapy: death, sensitivity. s, seconds.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Specificity (95% CI)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	0.58 (0.51 to 0.65)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	0.71 (0.61 to 0.79)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186 s	0.78 (0.73 to 0.83)
Sambola	2004[145]	Spain	100	CAD	Mono	CEPI	193 s	0.54 (0.44 to 0.63)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	0.73 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	0.73 (0.71 to 0.81)

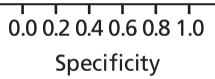

FIGURE 90 PFA-100®, monotherapy: death, specificity. s, seconds.

PFA-100®: major adverse cardiac events

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Sensitivity (95% CI)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (RAVE)	0.75 (0.38 to 0.94)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	298 s	First and second tertile vs. third tertile (RAVE)	1.00 (0.50 to 1.00)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (MACE)	0.45 (0.25 to 0.66)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	143 s	First and second tertile vs. third tertile (MACE)	0.75 (0.52 to 0.89)
Christaens	2008[127]	France	97	CAD	Mono	CEPI	187 s		0.36 (0.16 to 0.62)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186 s		0.29 (0.15 to 0.48)
Boncoraglio	2009[116]	Italy	129	CVD/ stroke	Mono	CEPI	165 s		0.21 (0.08 to 0.45)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s		0.00 (0.00 to 0.67)
Aksu	2009[109]	Turkey	220	UA/ACS	Mono at baseline; follow-up 73% mono, 27% dual	CEPI	170 s		0.59 (0.46 to 0.70)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s		0.55 (0.37 to 0.72)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Death, MI, or stroke	0.24 (0.14 to 0.38)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, or stroke	0.24 (0.14 to 0.38)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, stroke and revascularisation	0.23 (0.15 to 0.33)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Death, MI, stroke and revascularisation	0.23 (0.15 to 0.33)

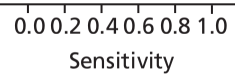

FIGURE 91 PFA-100®, monotherapy: MACEs, sensitivity. RAVE, recurrent acute vascular event; s, seconds.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Specificity (95% CI)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (RAVE)	0.68 (0.61 to 0.74)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	298 s	First and second tertile vs. third tertile (RAVE)	0.35 (0.28 to 0.42)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	143 s	First tertile vs. second and third tertile (MACE)	0.67 (0.60 to 0.74)
Addad	2010[108]	Tunisia/France	204	CAD	Mono	CEPI	298 s	First and second tertile vs. third tertile (MACE)	0.34 (0.28 to 0.41)
Christaens	2008[127]	France	97	CAD	Mono	CEPI	187 s		0.71 (0.60 to 0.80)
Pamukcu	2007[137]	Turkey	234	CAD	Mono	CEPI	186 s		0.79 (0.73 to 0.84)
Boncoraglio	2009[116]	Italy	139	CVD/ stroke	Mono	CEPI	165 s		0.80 (0.71 to 0.86)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s		0.66 (0.52 to 0.77)
Aksu	2009[109]	Turkey	220	UA/ACS	Mono at baseline; follow-up 73% mono, 27% dual	CEPI	170 s		0.69 (0.62 to 0.76)
Hobikoglu	2007[135]	Turkey	140	UA/ACS	Mono	CEPI	170 s		0.69 (0.60 to 0.78)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Death, MI, or stroke	0.77 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, or stroke	0.77 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Death, MI, stroke and revascularisation	0.76 (0.70 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Death, MI, stroke and revascularisation	0.76 (0.70 to 0.81)

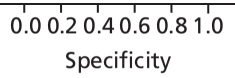

FIGURE 92 PFA-100®, monotherapy: MACEs, specificity. RAVE, recurrent acute vascular event; s, seconds.

PFA-100®: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Sensitivity (95% CI)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	MI	0.33 (0.04 to 0.85)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	Recurrent angina or silent ischaemia	0.63 (0.51 to 0.73)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	Stroke	0.33 (0.04 to 0.85)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Bypass surgery or TEA	0.67 (0.27 to 0.92)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	PTA/stenting	0.31 (0.12 to 0.59)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Peripheral arterial revascularisation	0.42 (0.23 to 0.64)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	Collagen/ADP	120 s	Recurrence	0.00 (0.00 to 0.38)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	CEPI	170 s	Recurrence	0.00 (0.00 to 0.38)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	MI	0.27 (0.13 to 0.49)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	MI	0.27 (0.13 to 0.49)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary angioplasty	0.24 (0.20 to 0.29)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary bypass surgery	0.31 (0.19 to 0.45)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Revascularisation	0.22 (0.10 to 0.41)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Revascularisation	0.22 (0.10 to 0.41)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	Stroke	0.00 (0.00 to 0.73)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Stroke	0.00 (0.00 to 0.73)

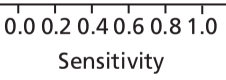

FIGURE 93 PFA-100®, monotherapy: ischaemic/thrombotic events, sensitivity. PTA, percutaneous transluminal angioplasty; s, seconds; TEA, thoracic epidural analgesia.

Study	Year	Country	Patients	Patient group	Therapy	Agonist	Threshold	Within-study difference	Specificity (95% CI)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	MI	0.70 (0.60 to 0.79)
Bevilacqua	2009[118]	Italy	202	CAD	Mono	CEPI	190 s	Recurrent angina or silent ischaemia	0.68 (0.60 to 0.76)
Christiaens	2008[127]	France	97	CAD	Mono	CEPI	187 s	Stroke	0.70 (0.60 to 0.79)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Bypass surgery or TEA	0.73 (0.59 to 0.83)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	PTA/stenting	0.68 (0.53 to 0.80)
Linnemann	2009[112]	Germany	57	PAD/PVD	Mono	CEPI	192 s	Peripheral arterial revascularisation	0.74 (0.58 to 0.85)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	Collagen/ADP	120 s	Recurrence	0.87 (0.72 to 0.94)
Ziegler	2002[150]	Austria	52	PAD/PVD	Mono	CEPI	170 s	Recurrence	0.87 (0.72 to 0.94)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	MI	0.77 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	MI	0.77 (0.71 to 0.81)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary angioplasty	0.75 (0.66 to 0.82)
Foussas	2009[115]	Greece	496	UA/ACS	Mono	CEPI	193 s	Coronary bypass surgery	0.76 (0.72 to 0.80)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Revascularisation	0.76 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	Unclear	Revascularisation	0.76 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	Collagen/ADP	Unclear	Stroke	0.76 (0.71 to 0.81)
Poulsen	2007[132]	Denmark	297	UA/ACS	Mono	CEPI	165 s	Stroke	0.76 (0.71 to 0.81)

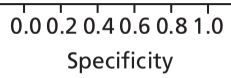

FIGURE 94 PFA-100®, monotherapy: ischaemic/thrombotic events, specificity. PTA, percutaneous transluminal angioplasty; s, seconds; TEA, thoracic epidural analgesia.

Whole-blood aggregometry: death

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Sensitivity (95% CI)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (1 µg)	Not clear	1.00 (0.19 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (0.5 µg)	Not clear	1.00 (0.19 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (2 µg)	Not clear	1.00 (0.19 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	AA (0.125 mM)	Not clear	1.00 (0.19 to 1.00)

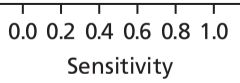

FIGURE 95 Whole-blood aggregometry, monotherapy: death, sensitivity. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Specificity (95% CI)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (1 µg)	Not clear	0.80 (0.52 to 0.92)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (0.5 µg)	Not clear	0.80 (0.52 to 0.92)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (2 µg)	Not clear	0.80 (0.52 to 0.92)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	AA (0.125 mM)	Not clear	0.80 (0.52 to 0.92)

FIGURE 96 Whole-blood aggregometry, monotherapy: death, specificity. AA, arachidonic acid.

Whole-blood aggregometry: major adverse cardiac events

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Sensitivity (95% CI)
Orta	2011[166]	Turkey	78	Miscellaneous	Mono	Multiplate	Not stated	Not stated	0.65 (0.43 to 0.82)

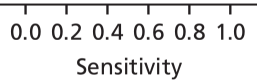

FIGURE 97 Whole-blood aggregometry, monotherapy: MACEs, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Specificity (95% CI)
Orta	2011[166]	Turkey	78	Miscellaneous	Mono	Multiplate	Not stated	Not stated	0.64 (0.51 to 0.75)

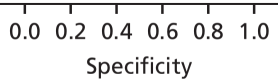

FIGURE 98 Whole-blood aggregometry, monotherapy: MACEs, specificity.

Whole-blood aggregometry: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Within-study difference	Sensitivity (95% CI)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	AA (0.5 mM)	6 ohms	Cerebral ischaemic event	0.36 (0.26 to 0.46)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	Collagen (1 µg)	10 ohms	Cerebral ischaemic event	0.55 (0.45 to 0.65)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (1 µg)	Not clear	MI	1.00 (0.11 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	AA (0.125 mM)	Not clear	MI	1.00 (0.11 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (2 µg)	Not clear	MI	1.00 (0.11 to 1.00)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (0.5 µg)	Not clear	MI	1.00 (0.11 to 1.00)

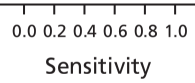

FIGURE 99 Whole-blood aggregometry, monotherapy: ischaemic/thrombotic events, sensitivity. AA, arachidonic acid.

Study	Year	Country	Patients	Patient group	Therapy	Test	Agonist	Threshold	Within-study difference	Specificity (95% CI)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	AA (0.5 mM)	6 Ω	Cerebral ischaemic event	0.90 (0.87 to 0.92)
Gengo	2008[128]	USA	653	CVD/stroke	Mono	Impedance	Collagen (1 µg)	10 Ω	Cerebral ischaemic event	0.89 (0.86 to 0.92)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (1 µg)	Not clear	MI	0.75 (0.49 to 0.89)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	AA (0.125 mM)	Not clear	MI	0.75 (0.49 to 0.89)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (2 µg)	Not clear	MI	0.75 (0.49 to 0.89)
Kaminska	2007[196]	Poland	17	UA/ACS	Mono	Impedance	Collagen (0.5 µg)	Not clear	MI	0.75 (0.49 to 0.89)

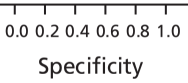

FIGURE 100 Whole-blood aggregometry, monotherapy: ischaemic/thrombotic events, specificity. AA, arachidonic acid.

Thromboelastography: death

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Cardiovascular death due to MI	1.00 (0.11 to 1.00)

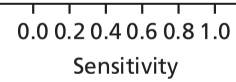

FIGURE 101 Thromboelastography, monotherapy: death, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Cardiovascular death due to MI	0.84 (0.78 to 0.89)

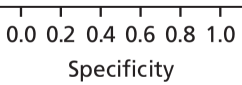

FIGURE 102 Thromboelastography, monotherapy: death, specificity.

Thromboelastography: ischaemic/thrombotic events

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Sensitivity (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	ACS with hospitalisation	0.45 (0.20 to 0.73)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Primary outcome events (ACS, death, recurrent treatment)	0.48 (0.30 to 0.67)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Recurrent interventional treatment	0.46 (0.22 to 0.72)

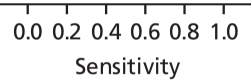

FIGURE 103 Thromboelastography, monotherapy: ischaemic/thrombotic events, sensitivity.

Study	Year	Country	Patients	Patient group	Therapy	Threshold	Within-study difference	Specificity (95% CI)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	ACS with hospitalisation	0.86 (0.80 to 0.91)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Primary outcome events (ACS, death, recurrent treatment)	0.90 (0.83 to 0.94)
Sahin	2011[168]	Turkey	168	CAD	Mono	50%	Recurrent interventional treatment	0.86 (0.80 to 0.91)

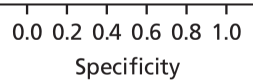

FIGURE 104 Thromboelastography, monotherapy: ischaemic/thrombotic events, specificity.

Appendix 4 Supplementary data

Owing to the extensive nature of the data extracted from the included studies for this project, it was deemed unfeasible to adequately present all the data in this report (even as appendices). The results section of the report contains, where necessary, details of the studies, including the populations studied, test characteristics and quality-related features, and data for key outcomes are presented in illustrative forest plots. However, this only applies for studies on patients being treated with aspirin as a single antiplatelet agent (monotherapy), and even so some data are omitted, including the numerical information that was used to produce the forest plots. Furthermore, data from studies in patients treated with dual (and triple) therapy, with aspirin as one of the agents, is completely omitted.

In the interest of transparency, the authors wish for all extracted and analytical data to be available to readers of this report. The data has been made available through a web portal which can be accessed via the following URL: http://medweb4.bham.ac.uk/NIHR_Aspirin_Resistance/

The data files available include Microsoft Excel spreadsheets of extracted data and statistical analysis, and specific data files used in Stata (StataCorp LP, College Station, TX, USA) to produce the forest plots presented in this report.

Below is an outline of the web portal indicating the files available for online viewing.

Project title: The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: a systematic review and economic evaluation

Project ref.: 10/36/02

Please find below links to the various data files relating to the project.

Data extraction tables

Data tables in Excel for all included studies where patients were receiving aspirin monotherapy at the time of platelet function testing. These data relate to studies reported in *Chapter 5* (section *Monotherapy*) of the HTA report.

Monotherapy-Included studies

Data tables in Excel for all included studies where patients were receiving aspirin dual therapy at the time of platelet function testing. These data relate to studies relevant to *Chapter 5*, *Dual therapy* in the HTA report.

Dual therapy-Included studies

Stata data files

Light transmission aggregometry for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using light transmission aggregometry (LTA) to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

LTA-monotherapy-all outcomes-unadjusted hazard ratios

LTA-monotherapy-all outcomes-adjusted hazard ratios

LTA-monotherapy-all outcomes-unadjusted odds ratios

LTA-monotherapy-all outcomes-adjusted odds ratios

LTA-monotherapy-all outcomes-sensitivity and specificity

VerifyNow for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using VerifyNow to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

VerifyNow-monotherapy-all outcomes-unadjusted hazard ratios

VerifyNow-monotherapy-all outcomes-adjusted hazard ratios

VerifyNow-monotherapy-all outcomes-unadjusted odds ratios

VerifyNow-monotherapy-all outcomes-adjusted odds ratios

VerifyNow-monotherapy-all outcomes-sensitivity and specificity

Thromboxane measurement for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using thromboxane to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

Thromboxane-monotherapy-all outcomes-unadjusted hazard ratios

Thromboxane-monotherapy-all outcomes-adjusted hazard ratios

Thromboxane-monotherapy-all outcomes-unadjusted odds ratios

Thromboxane-monotherapy-all outcomes-adjusted odds ratios

Thromboxane-monotherapy-all outcomes-sensitivity and specificity

PFA-100 for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using PFA-100 to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

PFA-100-monotherapy-all outcomes-unadjusted hazard ratios

PFA-100-monotherapy-all outcomes-adjusted hazard ratios

PFA-100-monotherapy-all outcomes-unadjusted odds ratios

PFA-100-monotherapy-all outcomes-adjusted odds ratios

PFA-100-monotherapy-all outcomes-sensitivity and specificity

Whole blood aggregometry for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using whole blood aggregometry to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

Whole Blood Aggregometry-all outcomes-unadjusted hazard ratios

Whole Blood Aggregometry-all outcomes-adjusted hazard ratios

Whole Blood Aggregometry-all outcomes-unadjusted odds ratios

Whole Blood Aggregometry-all outcomes-adjusted odds ratios

Whole Blood Aggregometry-all outcomes-sensitivity and specificity

Thromboelastography for monotherapy studies

The following links relate to the Stata data files used in the analysis of studies using TEG to measure platelet function in patients receiving aspirin monotherapy at the time of platelet function testing.

TEG-all outcomes-unadjusted hazard ratios

TEG-all outcomes-adjusted hazard ratios

TEG-all outcomes-unadjusted odds ratios

TEG-all outcomes-adjusted odds ratios

TEG-all outcomes-sensitivity and specificity

Appendix 5 List of unobtainable articles for prognostic/diagnostic utility systematic review

Barbano G, De Matteis F. [The thromboelastogram in the post-infarct period.] *Atti Soc Ital Cardiol* 1962;**22**:Comunicazioni 90–1.

Bogutskii BV, Ezhova VA, Shibanova ZN. [Thrombelastographic studies in patients with incipient cerebral atherosclerosis undergoing complex treatment.] *Vopr Kurortol Fizioter Lech Fiz Kult* 1971;**36**:504–7.

Bujold E, Tapp S, Giguere Y. Aspirin resistance and adverse pregnancy outcomes. *Neuroendocrinol Lett* 2011;**32**:369–70.

Fauknerova M, Osmancik P, Spacek M, Kejst L, Kalvach P. Aggregometry in secondary prevention of stroke. Aspirin resistance. *Ceska Slov Neurol Neurochir* 2011;**74**:527–32.

Fronescu E, Vilcu A. [Thromboelastographic investigations in atherosclerosis.] *Med Interna (Bucur)* 1962;**14**:1199–206.

Goelian P. Resistances to antiplatelet agents. *Rev Francoph Orthopt* 2010;**3**:12–16.

Gritsiuk AI. [Diagnosis of the pre-thrombotic state in cardiovascular diseases.] *Vrach Delo* 1971;**3**:8–14.

Haas T. Point of care diagnostic: thromboelastometry (ROTEM®). *Wien Klin Wochenschr* 2010;**122**(Suppl. 5):19–20.

Kwon SU. *Overcome Biochemical Aspirin Resistance Through Cilostazol Combination (ARCC)*. Stroke Trials Registry, Internet Stroke Center; 2007. URL: www strokecenter org/trials

Laguta PS, Katkova OV, Dobrovol'skii AB, Titaeva EV, Deev AD, Panchenko EP. Aspirin resistance in patients with stable ischemic heart disease. *Kardiologiia* 2010;**50**:4–11.

Liu L, Yang F, Li M, Hou H-J, Liu Y-H, Chen G-H, *et al.* Evaluation of the efficacy of anti-platelet aggregation drugs in patients using thromboelastograph after percutaneous transluminal angioplasty and stenting. *Chin J Cerebrovasc Dis* 2012;**9**:67–71.

Manus J-M. Aspirin resistance: How to detect it. *Actual Pharm* 2005;**440**:7.

Nidhinandana S, Changchit S. Prevalence of aspirin resistance in stroke patients in Phramongkutklao Hospital. *J Med Assoc Thai* 2010;**93**(Suppl. 6):51–4.

Okeahialiam BN, Ikeme AC. Suspected incidence of aspirin resistance. *West Afr J Med* 2010;**29**:129.

Petricevic M, Biocina B, Konosic S, Gasparovic H, Siric F, Burcar I. Early post coronary artery bypass grafting platelet hyperactivity, assessed by whole blood impedance aggregometry, indicates dual antiplatelet therapy. *Heart Surg Forum* 2011;**14**:S115.

Pregowski J, Przyluski J, Karcz M, Norwa-Otto B, Kruk M, Kalinczuk L, *et al.* Relation of subacute stent thrombosis and resistance to acetylsalicylic acid and clopidogrel in patients with acute coronary syndrome. Insights from the ANIN Myocardial Infarction Registry. *Postepy Kardiol Interwencyjnej* 2010;**6**:154–60.

Sinzinger H, Kritz H, Berent R, Schmid P, Steinbrenner D. Increased inflammatory activity rather than platelet function predicts events during acetylsalicylic acid (ASA) therapy for secondary prevention – a 10 years follow-up. Proceedings of the 20th International Congress on Thrombosis, Athens, 25–28 June 2008. pp. 87–91.

Tereshchenko OI. [Thrombelastogram in patients with coronary arteriosclerosis and auricular fibrillation.] *Vrach Delo* 1974;**0**:78–9.

Tulecki L, Gburek T. Aspirin resistance after cardiosurgical operations – Current review. *Pol Prz Chir* 2006;**78**:1193–204.

Wong S, Lewis D. Resistance to antiplatelet therapy: fact or fiction? *N Z Med J* 2005;**118**:U1459.

Appendix 6 Excluded articles for prognostic/diagnostic utility systematic review

TABLE 85 List of excluded articles with reason

Article	Reason for exclusion
Abderrazek F, Chakroun T, Addad F, Dridi Z, Gerotziafas G, Gamra H, *et al.* The GPIIIa PlA polymorphism and the platelet hyperactivity in Tunisian patients with stable coronary artery disease treated with aspirin. *Thromb Res* 2010;**125**:e265–8	D
Abuzahra M, Pillai M, Caldera A, Hartley WB, Gonzalez R, Bobek J, *et al.* Comparison of higher clopidogrel loading and maintenance dose to standard dose on platelet function and outcomes after percutaneous coronary intervention using drug-eluting stents. *Am J Cardiol* 2008;**102**:401–3	C
Ahmed N, Meek J, Davies GJ. Plasma salicylate level and aspirin resistance in survivors of myocardial infarction. *J Thromb Thrombolysis* 2010;**29**:416–20	D
Ahn SG, Lee SH, Sung JK, Kim JY, Yoon J. Intra-individual variability of residual platelet reactivity assessed by the VerifyNow-P2Y12 assay in patients with clopidogrel resistance after percutaneous coronary intervention. *Platelets* 2011;**22**:305–7	C
Ajjan R, Storey RF, Grant PJ. Aspirin resistance and diabetes mellitus. *Diabetologia* 2008;**51**:385–90	A
Aleil B, Jacquemin L, De PF, Zaehringer M, Collet JP, Montalescot G, *et al.* Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. *JACC Cardiovasc Interv* 2008;**1**:631–8	C
Aleil B, Meyer N, Cazenave JP, Mossard JM, Gachet C. High stability of blood samples for flow cytometric analysis of VASP phosphorylation to measure the clopidogrel responsiveness in patients with coronary artery disease. *Thromb Haemost* 2005;**94**:886–7	C, D
Alessi M-C, Cuisset T, Quilici J, Cohen W, Fourcade L, Grosdidier C, *et al.* Benefit of tailored therapy with high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel non responders undergoing coronary stenting for ACS. *J Thromb Haemost* 2011;**9**:48	D
Alessi M-C, Cuisset T, Quilici J, Grosdidier C, Fourcade L, Gaborit B, *et al.* High post-treatment platelet reactivity and impaired clinical prognosis but adequate response to thienopyridine in elderly patients with unstable coronary disease. *J Thromb Haemost* 2011;**9**:791	B, C
Alexander W, Price MJ, Mega JL. Platelet reactivity: The GRAVITAS trial. *P T* 2011;**36**:47	B, C
Alexopoulos D, Plakomyti T-E, Xanthopoulou I. Variability and treatment of high on-prasugrel platelet reactivity in patients with initial high on-clopidogrel platelet reactivity. *Int J Cardiol* 2012;**154**:333–4	A
Alfonso F, Angiolillo DJ. Platelet function assessment to predict outcomes after coronary interventions: hype or hope? *J Am Coll Cardiol* 2006;**48**:1751–4	A
Almsherqi ZA, McLachlan CS, Sharef SM. More on: enhanced antiplatelet effect of clopidogrel in patients whose platelets are least inhibited by aspirin: a randomized cross-over trial. *J Thromb Haemost* 2006;**4**:1638–9	A
Althoff TF, Fischer M, Knebel F, Langer E, Ziemer S, Baumann G. Elevated residual platelet reactivity to adenosine diphosphate and arachidonic acid in patients after myocardial infarction compared to patients after elective coronary stenting. *Eur Heart J* 2009;**30**:330	D
Altman R, Luciardi HL, Muntaner J, Herrera RN. The antithrombotic profile of aspirin. Aspirin resistance, or simply failure? *Thromb J* 2004;**2**:1–8	A
Ambrus JL, Ambrus CM, Akhter S. Aspirin 'allergy' and resistance. *J Am Coll Cardiol* 2004;**44**:939–40	A
Anand SS. Vascular viewpoint. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Eikelboom JW, Hirsh J, Weitz J, Johnston M, Yi Q, Yusuf S. *Circulation* 2002;**105**:1650–5	A

continued

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Andersen K, Hurlen M, Arnesen H, Seljeflot I. Aspirin non-responsiveness as measured by PFA-100 in patients with coronary artery disease. *Thromb Res* 2002;**108**:37–42	D
Andreassi MG, Adlerstein D, Coceani M, Shehi E, Vecoli C, Sampietro T, *et al.* High-risk single-nucleotide polymorphisms (SNPs) and genetic score on recurrent cardiovascular events following ischaemic heart disease. *Eur Heart J* 2011;**32**:947	B, C
Angiolillo DJ, Alfonso F. Platelet function testing and cardiovascular outcomes: steps forward in identifying the best predictive measure. *Thromb Haemost* 2007;**98**:707–9	A
Angiolillo DJ, Bernardo E, Sabate M, Jimenez-Quevedo P, Costa MA, Palazuelos J, *et al.* Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1541–7	C
Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, *et al.* Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012;**307**:265–74	C
Angiolillo DJ. Applying platelet function testing in clinical practice: What are the unmet needs? *JAMA* 2011;**306**:1260–1	A
Angiolillo DJ. Tackling the diabetic platelet: is high clopidogrel dosing the answer? *J Thromb Haemost* 2006;**4**:2563–5	A
Ankolekar S, Fox S, May J, Bath P. Assessing the efficacy of antiplatelet agents using remote testing of platelet P-selectin: preliminary observations from the triple antiplatelets for reducing dependency after ischaemic stroke (TARDIS) platelet sub study. *Platelets* 2010;**21**:395	D
Ann S-G, Lee S-H, Sung JK, Lee J-W, Youn Y-J, Kim J-Y, *et al.* High post-clopidogrel platelet reactivity assessed by VerifyNow P2Y12 assay doses not predict stent thrombosis in acute coronary syndromes. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E929	C
Anon. A mainstay drug underperforms. But a bedside test makes it easier to spot 'aspirin resistance'. *Heart Advisor* 2004;**7**:3	A
Anon. Aspirin resistance studied. *US Pharm* 1995;**20**:98	A
Anon. Aspirin resistance: a worry? *Johns Hopkins Medical Letter: Health After 50* 2005;**16**:1–2	A
Anon. I've been taking aspirin daily for 25 years, and clopidogrel for several years. In spite of this, I've had a number of heart attacks. You reported recently on people who can't benefit from aspirin, and I think I may be one of them. What should I do? *Heart Advisor* 2004;**7**:8	A
Anon. The importance of 'aspirin resistance'. *Aust J Pharm* 2009;**90**:77	A
Antoniucci D. Editorial comment: No role for triple antiplatelet therapy? *J Am Coll Cardiol* 2011;**57**:290–1	A
Aradf D, Rideg O, Vorobcsuk A, Horvath IG, Komocsi A. Impact of cytochrome P450 2C19 and ABCB1 genotypes on post-clopidogrel platelet reactivity and clinical outcome. *J Am Coll Cardiol* 2010;**56**(Suppl. 1):B1–2	C
Aradi D, Komocsi A, Vorobcsuk A, Rideg O, Tokes-Fuzesi M, Magyarlaki T, *et al.* Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. *Am Heart J* 2010;**160**:543–51	B, C
Aradi D, Komocsi A. Platelet function monitoring in patients on clopidogrel: what should we learn from GRAVITAS? *Platelets* 2012;**23**:167–76	A
Aradi D, Rideg O, Vorobcsuk A, Magyarlaki T, Magyari B, Konyi A, *et al.* Justification of 150 mg clopidogrel in patients with high on-clopidogrel platelet reactivity. *Eur J Clin Invest* 2012;**42**:384–92	C
Aradi D, Tokes-Fuzesi M, Paska T, Komocsi A. Monitoring the efficacy of antiplatelet therapy: all methods are equal, but some methods are more equal than others? *Am Heart J* 2008;**155**:e33	A
Aradi D, Vorobcsuk A, Pinter T, Konyi A, Magyari B, Horvath IG, *et al.* Doubling the maintenance dose of clopidogrel in patients with high post-clopidogrel platelet reactivity after percutaneous coronary intervention: the DOSER randomized, placebo-controlled trial. *Eur Heart J* 2010;**31**:970	B, C
Arai T, Endo A, Ikeda Y, Matsubara Y, Ogawa S, Ohono Y, *et al.* Impact of chronic kidney disease on platelet reactivity in patients with drug-eluting stent implantation. *Catheter Cardiovasc Interv* 2009;**73**:S77	C, D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Araullo MLC. Aspirin resistance among patients with recurrent non-cardioembolic stroke detected by rapid platelet function analyzer. *J Stroke Cerebrovasc Dis* 2008;**17**:2–8	D
Arazi HC, Doiny DG, Torcivia RS, Grancelli H, Waldman SV, Nojek C, *et al.* Impaired anti-platelet effect of aspirin, inflammation and platelet turnover in cardiac surgery. *Interact Cardiovasc Thorac Surg* 2010;**10**:863–7	D
Ari H, Aradi D, Komocsi A, Price MJ, Cuisset T, Hazarbasanov D, *et al.* Efficacy and safety of platelet function-guided antiplatelet therapy: systematic review and meta-analysis. *Int J Cardiol* 2012;**155**:S49–50	C
Artang R, Jensen E, Pedersen F, Frandsen NJ. Thrombelastography in healthy volunteers, patients with stable angina and acute chest pain. *Thromb Res* 2000;**97**:499–503	D
Ashbrook M, Schwatz J, Heroux A, Escalante V, Jeske W, Walenga J, *et al.* Platelet function in patients with a left ventricular assist device. *J Thromb Haemost* 2011;**9**:344	D
Awidi A, Saleh A, Dweik M, Kailani B, Abu-Fara M, Nabulsi R, *et al.* Measurement of platelet reactivity of patients with cardiovascular disease on-treatment with acetyl salicylic acid: a prospective study. *Heart Vessels* 2011;**26**:516–22. [Erratum published in *Heart Vessels* 2011;**26**:523]	D
Aydinalp A, Atar I, Altin C, Gulmez O, Atar A, Acikel S, *et al.* Platelet function analysis with two different doses of aspirin. *Turk Kardiyol Dernegi Ars* 2010;**38**:239–43	D
Aydinalp A, Atar I, Gulmez O, Atar A, Acikel S, Bozbas H, *et al.* The clinical significance of aspirin resistance in patients with chest pain. *Clin Cardiol* 2010;**33**:E1–7	D
Bach R, Jung F, Kohsiek I, Ozbek C, Spitzer S, Scheller B, *et al.* Factors affecting the restenosis rate after percutaneous transluminal coronary angioplasty. *Thromb Res* 1994;**74**(Suppl. 1):55–67	D
Balduini CL, Noris P, Bertolino G, Previtali M. Heparin modifies platelet count and function in patients who have undergone thrombolytic therapy for acute myocardial infarction. *Thromb Haemost* 1993;**69**:522–3	D
Baluda VP, Lakin KM, Pabvlishchuk SA, Deianov I, Nedelkovskii I. [Aspirin sensitivity of healthy persons and patients.] *Kardiologiia* 1981;**21**:55–7	C, D
Banti A, Mosialos L, Zarifis J, Kaprinis I, Vassara C, Kiskinis D, *et al.* Pharmacological resistance to clopidogrel (PRC) status is modified in time after percutaneous coronary intervention. A prospective study with repeated point of care monitoring with multiplate analyser. *J Thromb Haemost* 2009;**7**:587	C
Barbano G, Solera L. [On the control of anticoagulant therapy in myocardial infarct. Thromboelastography and quick's time: considerations and comparisons.] *Minerva Med* 1964;**55**:612–18	B
Barkagan ZS, Chernenko VF. [The significance of thromboelastography in obliterating diseases of the arteries of the extremities.] *Khirurgiia* (*Mosk*) 1969;**45**:60–5	B
Barragan P, Paganelli F, Camoin-Jau L, Bourguet N, Boulay-Moine D, Moulard M, *et al.* Validation of a novel ELISA-based VASP whole blood assay to measure P2Y12-ADP receptor activity. *Thromb Haemost* 2010;**104**:410–11	C
Basili S, Pignatelli P, Carnevale R, Di SS, Loffredo L, Violi F. PFA-100 A reliable tool to evaluate patients compliance to aspirin therapy. *J Thromb Haemost* 2009;**7**:883	D
Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with cardiovascular disease. *Circulation* 2005;**111**:e267–71	A
Beard K, Folia C, Liovas A. Platelet function tests are highly variable when used to identify patients resistant to clopidogrel. *Value Health* 2010;**13**:A342	B, C
Beer JH. Aspirin resistance for clinicians. *Curr Hematol Rep* 2004;**3**:149–50	A
Behr T, Kuch B, Behr W, von Scheidt W. Optimizing of thienopyridine therapy by multiple electrode platelet aggregometry in clopidogrel low responders undergoing PCI. *Clin Res Cardiol* 2011;**100**:907–14	C
Beigel R, Herscovici R, Fefer P, Hod H, Matetzky S. The anti-platelet effect of prasugrel as compared with clopidogrel in ST-elevation acute myocardial infarction patients undergoing primary angioplasty. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E480	C

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Berent R, Sinzinger H. 'Aspirin – resistance'? A few critical considerations on definition, terminology, diagnosis, clinical value, natural course of atherosclerotic disease, and therapeutic consequences. *Vasa* 2011;**40**:429–38	A
Berger CT, Wolbers M, Meyer P, Daikeler T, Hess C. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. *Rheumatology* 2009;**48**:258–61	C
Berger PB. Resistance to antiplatelet drugs: is it real or relevant? *Catheter Cardiovasc Interv* 2004;**62**:43–5	A
Berglund U, Wallentin L. Effects of ticlopidine on platelet function and on coronary insufficiency in patients with angina pectoris. *Adv Prostaglandin Thromboxane Leukot Res* 1985;**13**:277–80	D
Berkowitz SD, Frelinger AL, III, Hillman RS. Progress in point-of-care laboratory testing for assessing platelet function. *Am Heart J* 1998;**136**:S51–65	A
Bernal ME, Saban RJ. [Aspirin resistance.] *Med Clin* 2005;**124**:30–6	A
Bernlochner I, Byrne RA, Kastrati A, Sibbing D. The future of platelet function testing to guide therapy in clopidogrel low and enhanced responders. *Exp Rev Cardiovasc Ther* 2011;**9**:999–1014	A
Bertrand OF, Rodes-Cabau J, Rinfret S, Larose E, Bagur R, Proulx G, *et al.* Impact of final activated clotting time after transradial coronary stenting with maximal antiplatelet therapy. *Am J Cardiol* 2009;**104**:1235–40	C
Bezborod'ko BN, Batrak AA. [Thromboelastographic study of whole blood and oxalate plasma in patients with coronary arteriosclerosis in the ischemic stage.] *Ter Arkh* 1971;**43**:53–5	C
Bhatt DL. Aspirin resistance: more than just a laboratory curiosity. *J Am Coll Cardiol* 2004;**43**:1127–9	A
Bilsel T, Akbulut T, Yesilcimen K, Terzi S, Sayar N, Dayi SU, *et al.* Single high-dose bolus tirofiban with high-loading-dose clopidogrel in primary coronary angioplasty. *Heart Vessels* 2006;**21**:102–7	C
Biondi-Zoccai G, Lotrionte M. Aspirin resistance in cardiovascular disease. *BMJ* 2008;**336**:166–7	A
Bisdas T, Haverich A, Teebken OE. Letter by Bisdas, *et al.* regarding article, 'Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) trial'. *Circulation* 2011;**124**:e194–6	A
Blatt PM, Roberts HR. Letter: Platelet-function tests: predictive value. *New Engl J Med* 1975;**293**:611	A
Bochenek T, Wilczynski M, Wita K, Lelek M, Trusz-Gluza M, Bochenek A. [Evaluation of platelet response to antiplatelet drugs. An important clue for cardiologists and cardiosurgeons.] *Kardiol Pol* 2007;**65**:1266–9	A
Bocks M, Majahalme N, Russell M. Aspirin non-responsiveness, genetic polymorphisms in platelet aggregation, and the risk of thrombus formation in children with congenital heart disease. *Catheter Cardiovasc Interv* 2010;**76**:S14–15	B
Bonello L, Camoin-Jau L, Armero S, Com O, Arques S, Burignat-Bonello C, *et al.* Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *Am J Cardiol* 2009;**103**:5–10	C
Bonello L, Camoin-Jau L, Arques S, Boyer C, Panagides D, Wittenberg O, *et al.* Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 2008;**51**:1404–11	C
Bonello L, Camoin-Jau L, Dignat-George F, Paganelli F. A threshold of platelet reactivity for ischaemic events? *Eur Heart J* 2008;**29**:2185–6	A
Bonello L, Harouri K, Sabatier F, Camoin-Jau L, Arnaud L, Baumstarck-Barrau K, *et al.* Level of ADP receptor P2Y12 blockade during percutaneous coronary intervention predicts the extent of endothelial injury, assessed by CEC measurement. *Eur Heart J* 2010;**31**:976	B, C
Bonello L, Lemesle G, De Labriolle A, Roy P, Steinberg DH, Pinto Slottow TL, *et al.* Impact of a 600 mg loading dose of clopidogrel on 30-day outcome in unselected patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2008;**102**:1318–22	C
Bonello L, Paganelli F, Arpin-Bornet M, Auquier P, Sampol J, Dignat-George F, *et al.* Vasodilator-stimulated phosphoprotein phosphorylation analysis prior to percutaneous coronary intervention for exclusion of postprocedural major adverse cardiovascular events. *J Thromb Haemost* 2007;**5**:1630–6	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Bonello L, Pansieri M, Mancini J, Bonello R, Maillard L, Barnay P, *et al.* High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol* 2011;**58**:467–73	C
Bonten T, Snoep JD, Assendelft WJ, van der Meer V, Zwaginga JJ, Rosendaal FR, *et al.* Aspirin am or pm? A randomized cross-over trial. *J Thromb Haemost* 2011;**9**:334–5	A
Boos CJ, Lip GY. Platelet activation and cardiovascular outcomes in acute coronary syndromes. *J Thromb Haemost* 2006;**4**:2542–3	A
Bouman HJ, Breet NJ, Van Werkum JW, Zwart B, Ten CH, Hackeng CM, *et al.* Platelet reactivity in patients with coronary stent thrombosis. *Eur Heart J* 2010;**31**:973	D
Bouman HJ, van Werkum JW, Breet NJ, Ten CH, Hackeng CM, ten Berg JM. A case–control study on platelet reactivity in patients with coronary stent thrombosis. *J Thromb Haemost* 2011;**9**:909–16	D
Bradbury J. Aspirin resistance may increase death risk in some patients with heart disease. *Lancet* 2002;**359**:1128	A
Brar S, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim H-S, *et al.* Impact of clopidogrel on-treatment platelet reactivity on stent thrombosis after percutaneous coronary intervention: results from a collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1632	C
Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, *et al.* Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011;**58**:1945–54	C
Braunwald E, Angiolillo D, Bates E, Berger PB, Bhatt D, Cannon CP, *et al.* Antiplatelet therapy and platelet function testing. *Clin Cardiol* 2008;**31**(Suppl. 1):I36. [Erratum published in *Clin Cardiol* 2009;**32**:111]	A
Breet NJ, Bouman HJ, van Werkum JW, Ruven H, Hackeng CM, Berg JMT. First prospective comparison between platelet function tests in prediction of clinical outcome in 1100 patients undergoing coronary stent placement: Do point-of-care platelet function assays predict clinical outcomes in clopidogrel pretreated patients undergoing elective PCI (POPular study). *Circulation* 2010;**120**:2153	C
Breet NJ, De Jong C, Bos WJW, van Werkum JW, Bouman HJ, Kelder JC, *et al.* The impact of renal function on platelet reactivity and clinical outcome in patients undergoing percutaneous coronary intervention with stenting. *Eur Heart J* 2011;**32**:187	C
Breet NJ, Pittens CAC, Bouman HJ, van Werkum JW, ten Berg JM, Hackeng CM. The effect of platelet reactivity on infarct related artery patency in patients with ST-elevation myocardial infarction. *J Thromb Haemost* 2009;**7**:590	C
Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Hackeng CM, ten Berg JM. The relationship between platelet reactivity and infarct-related artery patency in patients presenting with a ST-elevation myocardial infarction. *Thromb Haemost* 2011;**106**:331–6	D
Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, *et al.* Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 2010;**303**:754–62. [Errata published in *JAMA* 2010;**303**:1257, *JAMA* 2011;**305**:2174, *JAMA* 2011;**305**:2172–3]	C
Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, ten Berg JM, Hackeng CM. Do not adjust the platelet count in light transmittance aggregometry when predicting thrombotic events after percutaneous coronary intervention. *J Thromb Haemost* 2010;**8**:2326–8	C
Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, ten Berg JM, Hackeng CM. Both peak and late aggregation are capable of identifying patients at risk for atherothrombotic events. *Thromb Haemost* 2011;**105**:197–9	C
Breet NJ. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 2011;**305**:2174	C
Briongos FS, Salido-Tahoces L, de Juan-Baguda J, Marti-Sanchez D. [Multiple arterial thrombosis and resistance to conventional antiaggregation.] *Rev Esp Cardiol* 2011;**64**:836–7	A

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Brister SJ, Buchanan MR. Aspirin 'resistance' and its impact on cardiovascular morbidity and mortality: it is real, clinically relevant and should be measured. *Heart* 2009;**95**:1223–4	A
Brizzio M, Shaw R, Sperling J, Grau J, Zapolanski A. Low responsiveness to clopidogrel therapy as a possible predictor for early failure of coronary percutaneous intervention requiring surgical revascularization. *Innov Technol Tech Cardiothorac Vasc Surg* 2011;**6**:190	B
Brizzio ME, Zapolanski A, Shaw RE, Collins M, Bosticco B, Sperling JS. The utilization of platelet inhibition tests in patients who receive preoperative clopidogrel reduces the waiting time for elective coronary surgery. *Innov Technol Tech Cardiothorac Vasc Surg* 2010;**5**:193	B
Broussalis E, Killer-Oberpfalzer M. Is multiple electrode platelet aggregometry beneficial in the management of carotid artery stenting? *Intervent Neuroradiol* 2011;**17**:210	B, C
Buchanan MR. Acetylsalicylic acid resistance and clinical outcome – the Hobikoglu study is worth noting. *Can J Cardiol* 2007;**23**:207–8	A
Bugnicourt JM, Roussel B, Garcia PY, Canaple S, Lamy C, Godefroy O. Aspirin non-responder status and early neurological deterioration: a prospective study. *Clin Neurol Neurosurg* 2011;**113**:196–201	D
Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Paniccia R, *et al.* Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;**49**:2312–17	C
Cairns JA, Eikelboom J. The pursuit of clinically relevant measures of platelet function after antiplatelet drug therapy. *J Am Coll Cardiol* 2008;**52**:1978–80	A
Calviere L, Voisin S, Coulon G, Viguier A, Sie P, Larrue V. Prevalence of low responsiveness to clopidogrel in patients with stroke or TIA. *Cerebrovasc Dis* 2011;**31**:259	D
Camilleri E, Jacquin L, Paganelli F, Bonello L. Personalized antiplatelet therapy: review of the latest clinical evidence. *Curr Cardiol Rep* 2011;**13**:296–302	A
Camoin-Jau L, Bonello L, Armero S, Com O, Barragan P, Paganelli F, *et al.* Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *J Thromb Haemost* 2009;**7**:589	C
Campo G, Ferraresi P, Marchesini J, Bernardi F, Valgimigli M. Relationship between paraoxonase Q192R gene polymorphism and on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention. *J Thromb Haemost* 2011;**9**:2106–8	C
Campo G, Parrinello G, Ferraresi P, Lunghi B, Tebaldi M, Miccoli M, *et al.* Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. *J Am Coll Cardiol* 2011;**57**:2474–83	C
Campo G, Valgimigli M, Gemmati D, Percoco G, Tognazzo S, Cicchitelli G, *et al.* Value of platelet reactivity in predicting response to treatment and clinical outcome in patients undergoing primary coronary intervention: insights into the STRATEGY Study. *J Am Coll Cardiol* 2006;**48**:2178–85	C
Can MM, Tanboga IH, Turkyilmaz E, Karabay CY, Akgun T, Koca F, *et al.* The risk of false results in the assessment of platelet function in the absence of antiplatelet medication: comparison of the PFA-100, multiplate electrical impedance aggregometry and verify now assays. *Thromb Res* 2010;**125**:e132–7	D
Cao J, Li XL, Fan L, Ye L. Single nucleotide polymorphisms of Ho-1 and Cox-1 are associated with complete aspirin resistance defined by light transmittance aggregation in the elderly. *Heart* 2011;**97**(Suppl. 3):A188	D
Capanni M, Prisco D, Antonucci E, Chiarugi L, Boddi V, Abbate R, *et al.* The pre-procedural platelet state predicts clinical recurrence after coronary angioplasty. *Int J Clin Lab Res* 1999;**29**:145–9	C
Capodanno D, Patel A, Dharmashankar K, Ferreiro JL, Ueno M, Kodali M, *et al.* Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. *Circ Cardiovasc Interv* 2011;**4**:180–7	D
Caron N, Rivard GE, Michon N, Morin F, Pilon D, Moutquin JM, *et al.* Low-dose ASA response using the PFA-100 in women with high-risk pregnancy. *J Obstet Gynaecol Can* 2009;**31**:1022–7	B, D
Carrie D, Garcia C, Gratacap MP, Voisin S, Payrastre B, Sie P. Assessment of platelet response to clopidogrel through measurement of ADP-induced Akt phosphorylation. *J Thromb Haemost* 2009;**7**:1411–13	C, D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Casassus F, Leroux L, James C, Sidibe S, Desplantes A, Naibo D, *et al.* Response to prasugrel in ST elevation myocardial infarction patients: Is it as rapid as we expected? *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B43–4	B, C
Cassiano O, Mairano C. [Considerations and research on the relations between chronic peripheral arteriopathy and blood coagulation.] *Minerva Cardioangiol* 1963;**11**:510–15	B
Cattaneo M. [Tailored treatment with clopidogrel based on the results of platelet function tests should not be implemented, in the absence of clear indications on the methodology to be used.] *G Ital Cardiol* 2011;**12**:172–3	B, C
Cattaneo M. Laboratory detection of 'aspirin resistance': what test should we use (if any)? *Eur Heart J* 2007;**28**:1673–5	A
Cayla G, Macia JC, Rabesandratana H, Roubille F, Gervasoni R, Pasquie JL, *et al.* Flow cytometric assessment of vasodilator-stimulated phosphoprotein: prognostic value of recurrent cardiovascular events after acute coronary syndromes. *Arch Cardiovasc Dis* 2008;**101**:743–51	C
Cepelakova H, Cepelak V, Sova J. [Prognostic significance of some coagulation changes in myocardial infarct.] *Vnitr Lek* 1973;**19**:478–86	B
Chen H. Randomized comparison of adjunctive Naoxintong versus standard maintenance dose clopidogrel in patients with CYP2C19*2 gene mutation: results of the ABNJC-CYP2C19*2 (Adjunctive Buchang Naoxintong Jiaonang Versus Standard Maintenance Dose Clopidogrel in Patients with CYP2C19*2 Gene Mutation) randomized study. *Int J Cardiol* 2011;**152**:S26	B, C
Chen L, Bracey AW, Radovancevic R, Cooper JR, Jr, Collard CD, Vaughn WK, *et al.* Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2004;**128**:425–31	C, D
Chen W-H, Lee P-Y, Ng W, Kwok JYY, Cheng X, Lee SWL, *et al.* Relation of aspirin resistance to coronary flow reserve in patients undergoing elective percutaneous coronary Intervention. *Am J Cardiol* 2005;**96**:760–3	D
Chen W-H, Lee P-Y, Ng W, Tse H-F, Lau C-P. Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 2004;**43**:1122–6	D
Chen W-H, Lee P-Y. Reply to 'comments in response to low-dose aspirin increases aspirin resistance in patients with coronary artery disease'. *Am J Med* 2006;**119**:287–8	A
Chen YW, Lee KY, Li CH, Lin YY, Yang CD, Hsieh CF, *et al.* Difference in platelet function test could predict prognosis in the acute stage of ischemic stroke. *Cerebrovasc Dis* 2011;**31**:281–2	D
Chen ZQ. Influence of Ranitidine on gastrointestinal hemorrhage and thrombosis caused by dual antiplatelet therapy after PCI in patients with coronary heart disease. *Cardiology* 2010;**117**:48–9	C
Chiesa FT. [Thromboelastography in coronary heart disease: evaluations provided of the blood coagulation situation; indications for therapy.] *G Gerontol* 1971;**19**:800–4	B
Choi DH, Suh JW, Park KW, Kang HJ, Kim HS. Assessment of the bioequivalence of brand and biogeneric formulations of abciximab for the treatment of acute coronary syndrome: a prospective, open-label, randomized, controlled study in Korean patients. *Clin Ther* 2009;**31**:1804–11	B, C
Cholette JM, Mamikonian L, Alfieris GM, Blumberg N, Lerner NB. Aspirin resistance following pediatric cardiac surgery. *Thromb Res* 2010;**126**:200–6	B
Chooi JL, Vesamia SA, Gama CA, Szecowka-Harte SR, Brown V. Thromboelastography in prediction of blood loss after cardiac surgery. *Eur J Anaesthesiol* 2011;**28**:84	D
Chow SL, Cheung RJ. Aspirin resistance: a growing concern. *Formulary* 2006;**41**:192–201	A
Christiaens L, Allal J, Brizard A, Macchi L. Aspirin resistance: a reality? *Med Ther* 2003;**9**:181–6	A
Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, *et al.* Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010;**8**:148–56	B, C, D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Clappers N, van Oijen MG, Sundaresan S, Brouwer MA, Te Morsche RH, Keuper W, *et al.* The C50T polymorphism of the cyclooxygenase-1 gene and the risk of thrombotic events during low-dose therapy with acetyl salicylic acid. *Thromb Haemost* 2008;**100**:70–5	C
Cocozza M, Milani M, Picano T, Oliviero U, Russo N, Coto V. Antiaggregatory effects of picotamide in long-term treatment: a 2-year, double-blind placebo-controlled trial. *Vasc Med* 1997;**2**:292–5	B
Cohen AH, Doiny D, Waldman SV, Spampinato TR, Grancelli H, Miriuka S, *et al.* Association between reduced aspirin inhibition and platelet turnover in cardiac surgery. *Eur Heart J* 2009;**30**:916–17	D
Cohen M, Merino A, Hawkins L, Greenberg S, Fuster V. Clinical and angiographic characteristics and outcome of patients with rest-unstable angina occurring during regular aspirin use. *J Am Coll Cardiol* 1991;**18**:1458–62	C
Collet JP, Cayla G, Cuisset T, Elhadad S, Range G, Vicaut E, *et al.* Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J* 2011;**161**:5–12	A
Collet J-P, Hulot JS, Pena ANA, Vilard ERIC, Esteve JB, Cayla G, *et al.* Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: impact on clinical events and on. *Eur Heart J* 2009;**30**:906	B, C
Combescure C, Fontana P, Mallouk N, Berdague P, Labruyere C, Barazer I, *et al.* Clinical implications of clopidogrel non-response in cardiovascular patients: a systematic review and meta-analysis. *J Thromb Haemost* 2010;**8**:923–33	C
Conti CR. Is aspirin resistance a risk factor? *Clin Cardiol* 2005;**28**:163–4	A
Cordina SM, Vazquez G, Suri MF, Lakhsminarayan K, Qureshi Z. Does aspirin failure increase the chances of recurrent stroke and/or death among patients with ischemic stroke: a pooled analysis of two prospective trials. *Stroke* 2010;**41**:e214	C
Cotton JM, Worrall AM, Hobson AR, Smallwood A, Amoah V, Dunmore S, *et al.* Individualised assessment of response to clopidogrel in patients presenting with acute coronary syndromes: a role for short thrombelastography? *Cardiovasc Ther* 2010;**28**:139–46. [Erratum published in *Cardiovasc Ther* 2010;**28**:254. Rajendra R (corrected to Raghuraman RP)]	C
Cowley MJ, Kuritzky L. Developments in antiplatelet therapy for acute coronary syndromes and considerations for long-term management. *Curr Med Res Opin* 2009;**25**:1477–90	C
Cox D. Aspirin resistance: a nebulous concept. *J Clin Pharmacol Pharm* 2010;**1**:39–47	A
Crescente M, Di Castelnuovo A, Iacoviello L, De Gaetano G, Cerletti C. PFA-100 closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: a meta-analysis of 19 studies comprising 3,003 patients. *Thromb Haemost* 2008;**99**:1129–31	A
Cubero JM. Candy study: minor myocardial damage in patients with type 2 diabetes mellitus and dual hypo-responsiveness to aspirin and clopidogrel with Xience V stent implantation. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E488	D
Cuisset T, Frere C, Quilici J, Gaborit B, Castelli C, Poyet R, *et al.* Predictive values of post-treatment adenosine diphosphate-induced aggregation and vasodilator-stimulated phosphoprotein index for stent thrombosis after acute coronary syndrome in clopidogrel-treated patients. *Am J Cardiol* 2009;**104**:1078–82	C
Cuisset T, Frere C, Quilici J, Morange PE, Mouret JP, Bali L, *et al.* Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. *JACC Cardiovasc Interv* 2008;**1**:649–53	C
Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Carvajal J, *et al.* Benefit of a 600 mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 2006;**48**:1339–45	C
Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Mielot C, *et al.* High post-treatment platelet reactivity is associated with a high incidence of myonecrosis after stenting for non-ST elevation acute coronary syndromes. *Thromb Haemost* 2007;**97**:282–7	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Cuisset T, Frere C, Quilici J, Poyet R, Bali L, Morange PE, *et al.* Glycoprotein IIbIIIa inhibitors improve clinical outcome after coronary stenting in clopidogrel non responders: a prospective, randomized study. *Arch Cardiovasc Dis Suppl* 2010;**2**:13	C
Cuisset T, Hamilos M, Sarma J, Sarno G, Wyffels E, Vanderheyden M, *et al.* Relation of low response to clopidogrel assessed with point-of-care assay to periprocedural myonecrosis in patients undergoing elective coronary stenting for stable angina pectoris. *Am J Cardiol* 2008;**101**:1700–3	D
Cuisset T, Morange P-E, Alessi M-C. High residual platelet reactivity and thrombotic events. *JAMA* 2011;**306**:2561	A, B, C
Cuisset T, Quilici J, Fugon L, Cohen W, Roux P, Gaborit B, *et al.* Non-adherence to aspirin in patients undergoing coronary stenting: negative impact of comorbid conditions and implications for clinical management. *Arch Cardiovasc Dis* 2011;**104**:306–12	D
Cuisset T, Quilici J, Grosdidier C, Fourcade L, Gaborit B, Pankert M, *et al.* Comparison of platelet reactivity and clopidogrel response in patients ≤ 75 years versus > 75 years undergoing percutaneous coronary intervention for non-ST-segment elevation acute coronary syndrome. *Am J Cardiol* 2011;**108**:1411–16	C
Curzen N, Sambu N. Interventional cardiology: Antiplatelet therapy in percutaneous coronary intervention: is variability of response clinically relevant? *Heart* 2011;**97**:1433–40	A
Dai Y, Lee A, Critchley LA, White PF. Does thromboelastography predict postoperative thromboembolic events? A systematic review of the literature. *Anesth Analg* 2009;**108**:734–42	B, C
Dalal AR, D'Souza S, Shulman MS. Brief review: coronary drug-eluting stents and anesthesia. *Can J Anaesth* 2006;**53**:1230–43	C
Dalal JJ, Bloom A, Henderson AH. Transmyocardial platelet behavior in CAD. *Circulation* 1981;**63**:969–70	B, C, D
Dalal JJ, Penny WJ, Saunders KC, Sheridan DJ, Bloom AL, Henderson AH. Platelet counts and aggregates in coronary artery disease. *Eur Heart J* 1982;**3**:107–13	C, D
Dale J, Myhre E, Loew D. Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement. *Am Heart J* 1980;**99**:746–52	C
Dalen JE. Aspirin resistance: is it real? Is it clinically significant? *Am J Med* 2007;**120**:1–4	A
Dalen JE. Is aspirin resistance due to noncompliance? *Arch Intern Med* 2008;**168**:550	A
Dalen M, Van Der Linden J, Lindvall G, Ivert T. Correlation between point-of-care platelet function testing and bleeding after coronary artery surgery. *Scand Cardiovasc J* 2012;**46**:32–8	D
D'Andrea D, Furbatto F, Boccalatte M, Scarpelli M. Use of point-of-care testing to assess optimal antiplatelet therapy when a nasogastric tube is the only way of administration. *Int J Cardiol* 2011;**147**:S67	D
Darcy MD, Kanterman RY, Kleinhoffer MA, Vesely TM, Picus D, Hicks ME, *et al.* Evaluation of coagulation tests as predictors of angiographic bleeding complications. *Radiology* 1996;**198**:741–4.	C
Davlouros PA, Arseniou A, Hahalis G, Chiladakis J, Mazarakis A, Damelou A, *et al.* Timing of clopidogrel loading before percutaneous coronary intervention in clopidogrel-naive patients with stable or unstable angina: a comparison of two strategies. *Am Heart J* 2009;**158**:585–91	C
Dawson J, Quinn TJ, Rafferty M, Ray G, Walters MR, Lees KR. Aspirin resistance in patients with recent stroke: a case–control study. *Cerebrovasc Dis* 2009;**27**:45	D
De Gaetano G, Cerletti C. Aspirin resistance: a revival of platelet aggregation tests? *J Thromb Haemost* 2003;**1**:2048–50	A
De Gaetano G. Aspirin resistance in diabetic patients. *Diabetes Care* 2004;**27**:1244–5	A
De Matteis F, Barbano G. [The thrombelastogram in coronary disease.] *Minerva Med* 1963;**54**:194–202	B, D
de Miguel CA, Cuellas RC, Diego NA, Samaniego LB, Alonso RD, Fernandez VF, *et al.* Post-treatment platelet reactivity predicts long-term adverse events better than the response to clopidogrel in patients with non-ST-segment elevation acute coronary syndrome. *Rev Esp Cardiol* 2009;**62**:126–35	C

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
de Miguel Castro A, Diego Nieto A, Perez de Prado A. Letter by de Miguel Castro, *et al.* regarding article, 'cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up'. *Circulation* 2009;**120**:e98	A
De Miguel Castro A, Nieto AD, Perez de Prado A. Letter by De Miguel Castro, *et al.* regarding article, 'Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the gauging responsiveness with a VerifyNow P2Y12 assay: impact on Thrombosis and Safety (GRAVITAS) trial'. *Circulation* 2012;**125**:e570	A
De Rosa R, Galasso G, Piscione F, Santulli G, Iaccarino G, Piccolo R, *et al.* Increased risk of cardiovascular events associated with the GPIIIA PlA2 polymorphism. *Cardiovasc Res* 2010;**87**:S74–5	C
Dekhtiar' AL, Synovets AS. [Thromboelastogram data in patients with thromboobliterating diseases of the vessels.] *Vrach Delo* 1967;**5**:45–7	C, D
Deliargyris EN, Boudoulas H. Aspirin resistance. *Hell J Cardiol* 2004;**45**:1–5	A
Dengler R, Lichtinghagen R, Schumacher H, Weissenborn K, Worthmann H. C-reactive protein and its pharmacologic reduction as predictor of outcome in the early treatment with aspirin and extended-release dipyridamole versus low dose aspirin alone for TIA/ischemic stroke within 24 hour of symptom-onset (EARLY-Trial). *Stroke* 2010;**41**:e261	C
D'Erasmo E, Aliberti G, Celi FS, Vecci E, Mazzuoli G. [Sequential evaluation of platelet count and mean platelet volume during myocardial infarction.] *Medicina* 1988;**8**:58–60	B, D
D'Erasmo E, Aliberti G, Celi FS, Vecci E, Romagnoli E, Mazzuoli G. [Changes in several blood platelet parameters in cerebral infarct.] *Recenti Prog Med* 1988;**79**:12–14	B, C, D
D'Erasmo E. [Relationship between number and volume of circulating blood platelets in cerebral and myocardial infarct.] *Recenti Prog Med* 1990;**81**:675–6	A, C, D
Dhatariya KK. Aspirin for everyone over 50? Don't forget aspirin resistance. *BMJ* 2005;**331**:161	A
Di Giovanni V, Agrifoglio G. [Thrombelastographic observations in the postoperative period and its value in the prevention of thrombophletitic complications.] *Minerva Chir* 1963;**18**:299–311	B, D
Di Minno G, Violi F. Aspirin resistance and diabetic angiopathy: back to the future. *Thromb Res* 2004;**113**:97–9	A
Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A, *et al.* Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol* 2010;**56**:550–7	C
Dietrich GV, Schueck R, Menges T, Kiesenbauer NP, Fruehauf AC, Marquardt I. Comparison of four methods for the determination of platelet function in whole blood in cardiac surgery. *Thromb Res* 1998;**89**:295–301	B, D
Dmoszynska-Giannopoulou A, Pluta A, Kowalewski J. [Platelet function and lipid disorders in diabetics.] *Pol Arch Med Wewn* 1979;**62**:293–7	B, D
Dmoszynska-Giannopoulou A. [Function and coagulative activity of blood platelets in patients with attacks of transient cerebral ischemia.] *Polski Tygodnik Lekarski* 1984;**39**:1569–71	B, D
Doraiswamy VA. Letter by Doraiswamy regarding article, 'Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study'. *Circulation* 2010;**121**:e235	A
Drouet L, Bal dit SC, Henry P. [The basis of platelets: platelets and atherothrombosis: an understanding of the lack of efficacy of aspirin in peripheral arterial disease (PAD) and diabetic patients.] *Drugs* 2010;**70**(Suppl 1.):9–14	A
Drouet L. [Is aspirin resistance a reality?] *Rev Med Interne* 2004;**25**:101–3	A
Drzewoski J, Watala C. Is aspirin resistance a real problem in people with type 2 diabetes? *Diabetes Care* 2004;**27**:1245–6	D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
d'Udekem Y. The devastating consequences of thrombosis of systemico pulmonary shunts and the blind administration of aspirin. *Thromb Res* 2010;**126**:163	A
Dyszkiewicz-Korpanty AM, Kim A, Burner JD, Frenkel EP, Sarode R. Comparison of a rapid platelet function assay – Verify Now Aspirin – with whole blood impedance aggregometry for the detection of aspirin resistance. *Thromb Res* 2007;**120**:485–8	B, D
Eikelboom J, Oldgren J, Reilly P, Yusuf S, Wallentin L, Ezekowitz M, *et al.* No evidence of platelet activation in patients with atrial fibrillation who are treated with dabigatran: a substudy of the rely trial. *J Thromb Haemost* 2011;**9**:346	D
Eikelboom J. Aspirin resistance: does it exist and is it an important clinical problem? *Clin Adv Haematol Oncol* 2006;**4**:268–70	A
Eikelboom JW, Emery J, Hankey GJ. The use of platelet function assays may help to determine appropriate antiplatelet treatment options in a patient with recurrent stroke on baby aspirin: against. *Stroke* 2010;**41**:2398–9	A
Eikelboom JW, Hankey GJ. Aspirin resistance: a new independent predictor of vascular events? *J Am Coll Cardiol* 2003;**41**:966–8	A
El Ghannudi S, Ohlmann P, Jesel L, Radulescu B, El Adraa E, Crimizade U, *et al.* Impaired inhibition of P2Y (12) by clopidogrel is a major determinant of cardiac death in diabetes mellitus patients treated by percutaneous coronary intervention. *Atherosclerosis* 2011;**217**:465–72	C
El Ghannudi S, Ohlmann P, Meyer N, Wiesel ML, Radulescu B, Chauvin M, *et al.* Impact of P2Y12 inhibition by clopidogrel on cardiovascular mortality in unselected patients treated by percutaneous coronary angioplasty: a prospective registry. *JACC Cardiovasc Interv* 2010;**3**:648–56	C
El Ghannudi S, Ohlmann P, Wiesel ML, Radulescu B, Bareiss P, Chauvin M, *et al.* Impact of platelet poor responsiveness to clopidogrel on cardiovascular outcome in type 2 Diabetes mellitus patients treated by percutaneous coronary angioplasty. *Eur Heart J* 2009;**30**:194	B, C
El Ghannudi S, Ohlmann P, Wiesel ML, Radulescu B, Bareiss P, Chauvin M, *et al.* Platelet reactivity assessed by flow cytometric VASP phosphorylation is an independent predictor of death and cardiovascular death in unselected patients undergoing PCI. *Eur Heart J* 2009;**30**:192–3	B, C
Lu TQ, Mu DJ, Tang YD, Chen J, Yuan JQ, Wu YJ, *et al.* The clopidogrel response is associated with clinical outcomes of the CHD patients who underwent elective PCI. *Cardiology* 2010;**117**:58–9	B
Elwood P, Morgan G. Aspirin resistance: what is the risk of cardiovascular morbidity? *BMJ* 2008;**336**:291	A
Elwood PC, Beswick A, Pickering J, McCarron P, O'Brien JR, Renaud SR, *et al.* Platelet tests in the prediction of myocardial infarction and ischaemic stroke: evidence from the Caerphilly Prospective Study. *Br J Haematol* 2001;**113**:514–20	C
Elwood PC, Renaud S, Beswick AD, O'Brien JR, Sweetnam PM. Platelet aggregation and incident ischaemic heart disease in the Caerphilly cohort. *Heart* 1998;**80**:578–82	B
Elwood PC, Renaud S, Sharp DS, Beswick AD, O'Brien JR, Yarnell JW. Ischemic heart disease and platelet aggregation. The Caerphilly Collaborative Heart Disease Study. *Circulation* 1991;**83**:38–44	B
Eng M, Hudson PA, Endemann S, Barker C, Williams M, Levisay J, *et al.* Low on-treatment reactivity with clopidogrel does not significantly impact bleeding complications in patients receiving dual anti-platelet therapy. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1635	C
Epimakhova OV, Sumarokov AV. [Functional activity of thrombocytes in myocardial diseases.] *Kardiologiia* 1983;**23**:32–5	B, C, D
Erlinge D, Berg JT, Foley D, Angiolillo D, Brown P, Wagner H, *et al.* Prasugrel 5 mg in low body weight patients reduces platelet reactivity to a similar extent as prasugrel 10 mg in higher body weight patients: results from the feather trial. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E341	C
Esposito G. Responsiveness to P2Y12 receptor inhibitors. *Curr Opin Cardiol* 2011;**26**(Suppl. 1):S31–7	A
Eto K, Ochiai M, Isshiki T, Takeshita S, Terakura M, Sato T, *et al.* Platelet aggregability under shear is enhanced in patients with unstable angina pectoris who developed acute myocardial infarction. *Jpn Circ J* 2001;**65**:279–82	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Ettinger MG. Thromboelastographic studies in cerebral infarction. *Stroke* 1974;**5**:350–4	B, D
Lindhoff-Last E. Non-compliance and genetic polymorphisms: when patients do not respond to ASA or clopidogrel. *Dtsch Apoth Ztg* 2010;**150**:59–60	A
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Faraday N, Braunstein JB, Heldman AW, Bolton ED, Chiles KA, Gerstenblith G, *et al.* Prospective evaluation of the relationship between platelet–leukocyte conjugate formation and recurrent myocardial ischemia in patients with acute coronary syndromes. *Platelets* 2004;**15**:9–14	D
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Fattorutto M, Pradier O, Schmartz D, Ickx B, Barvais L. Does the platelet function analyser (PFA-100) predict blood loss after cardiopulmonary bypass? *Br J Anaesth* 2003;**90**:692–3	B, D
Fefer P, Beigel R, Shenkman B, Gannot S, Varon D, Savion N, *et al.* Evaluation of platelet response to different clopidogrel dosing regimens in patients with acute coronary syndrome in clinical practice. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E484	B, C, D
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Feher G, Koltai K, Papp E, Alkonyi B, Solyom A, Kenyeres P, *et al.* Aspirin resistance: possible roles of cardiovascular risk factors, previous disease history, concomitant medications and haemorrheological variables. *Drugs Aging* 2006;**23**:559–67	D
Feher G, Pusch G, Szapary L. Optical aggregometry and aspirin resistance. *Acta Neurol Scand* 2009;**119**:139	A
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Fitscha P, Sinzinger H. [Defects in the prostaglandin system. VII. (Generalized, inherited [?]) cyclooxygenase defect.] *Wien Klin Wochenschr* 1988;**100**:711–15	A
FitzGerald GA. Parsing an enigma: the pharmacodynamics of aspirin resistance. *Lancet* 2003;**361**:542–4	A
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Fong J, Cheng-Ching E, Hussain MS, Katzan I, Gupta R. Predictors of biochemical aspirin and clopidogrel resistance in patients with ischemic stroke. *J Stroke Cerebrovasc Dis* 2011;**20**:227–30	D
Fontana P, Berdague P, Castelli C, Nolli S, Barazer I, Fabbro-Peray P, *et al.* Clinical predictors of dual aspirin and clopidogrel poor responsiveness in stable cardiovascular patients from the ADRIE study. *J Thromb Haemost* 2010;**8**:2614–23	D
Fontana P, Reber G, de Moerloose P. Assessing aspirin responsiveness using the Verify Now Aspirin assay. *Thromb Res* 2008;**121**:581–2	B, C, D
Fontana P, Remones V, Reny JL, Aiach M, Gaussem P. P2Y1 gene polymorphism and ADP-induced platelet response. *J Thromb Haemost* 2005;**3**:2349–50	B, C, D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
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Foo F, Oldroyd KG. Clinical value of antiplatelet therapy in patients with acute coronary syndromes and in percutaneous coronary intervention. *Biomarkers Med* 2011;**5**:9–30	A
Forestier F, Belisle S, Contant C, Harel F, Janvier G, Hardy JF. [Reproducibility and interchangeability of the Thromboelastograph, Sonoclot and Hemochron activated coagulation time in cardiac surgery.] *Can J Anaesth* 2001;**48**:902–10	D
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Frelinger AL, III, Michelson AD. Clopidogrel linking evaluation of platelet response variability to mechanism of action. *J Am Coll Cardiol* 2005;**46**:646–7	A
Frelinger AL, III. Platelet reactivity with prolonged aspirin treatment – steady going at 2 year. *Circ J* 2010;**74**:1077–8	A
Frelinger AL, III, Furman MI, Linden MD, Li Y, Fox ML, Barnard MR, *et al.* Response to letter regarding article, 'Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700-patient study of aspirin resistance'. *Circulation* 2007;**115**:e46	A
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Frere C, Cuisset T, Quilici J, Gaborit B, Poyet R, Bali L, *et al.* Predictive ability of post treatment ADP-induced aggregation and VASP index on stent thrombosis after acute coronary syndrome in clopidogrel-treated patients: a prospective study. *J Thromb Haemost* 2009;**7**:585	B, C
Freynhofer M, Brozovic I, Bruno V, Leherbauer L, Djurkovic M, Jarai R, *et al.* Routine determination of platelet reactivity in patients on long-term dual antiplatelet therapy: The WILMAA Registry. *Eur Heart J Suppl* 2010;**12**:F65	C, D
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Friend M, Vucenik I, Miller M. Platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ* 2003;**326**:82–3	D
Fritsma GA, Ens GE, Alvord MA, Carroll AA, Jensen R. Monitoring the antiplatelet action of aspirin. *JAAPA* 1961;**14**:57–8	B, D
Fukushima K, Kobayashi Y, Kitahara H, Iwata Y, Kuroda N, Ooyama M, *et al.* Effect of 450 mg loading dose of clopidogrel on platelet function in Japanese patients undergoing coronary stent placement. *Heart Vessels* 2010;**25**:182–6	C
Gabriel SA, Beteli CB, Tanighuchi RS, Tristao CK, Gabriel EA, Job JR. Aspirin resistance and atherothrombosis. *Rev Bras Cir Cardiovasc* 2007;**22**:96–103	A
Gaglia MA, Torguson R, Pakala R, Sardi G, Xue Z, Suddath WO, *et al.* Patients with acute coronary syndromes undergoing percutaneous coronary intervention have higher levels of on-treatment platelet reactivity. *Circulation* 2011;**124**(Suppl. 1):A9814	C, D
Gaglia MA, Torguson R, Sardi G, Xue Z, Suddath WO, Kent KM, *et al.* Patients with acute coronary syndrome have higher levels of on-treatment platelet reactivity. *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B48–9	C, D
Gaglia MA, Torguson R, Xue Z, Pakala R, Gonzalez MA, Ben-Dor I, *et al.* Periprocedural myocardial infarction and high on-treatment platelet reactivity. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1897	C

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
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Galvani M. High postclopidogrel platelet reactivity in non-ST-elevation acute coronary syndrome treated with stenting: a clue for adverse prognosis? *J Thromb Haemost* 2006;**4**:536–8	A
Gao F, Wang ZX, Men JL, Ren J, Wei MX. Effect of polymorphism and type II diabetes on aspirin resistance in patients with unstable coronary artery disease. *Chin Med J* 2011;**124**:1731–4	D
Gao L, Li YJ, Chen KY. [Effects of supplementing qi and activating blood circulation method on platelet aggregation rate, adhesion rate and thromboxane B2 level in patients with stable angina pectoris and intolerable to aspirin.] *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2008;**28**:300–3	B
Garcia-Rinaldi R. Thromboprophylaxis with antiplatelet agents prevents cerebral thromboembolism in patients with mechanical aortic prostheses. *Stroke* 2011;**42**:e345	B
Gasparovic H, Petricevic M, Biocina B. Letter by Gasparovic, *et al.* regarding article, 'Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) trial'. *Circulation* 2011;**124**:e193–6	A
Gasparovic H, Petricevic M, Biocina B. Reduction of thienopyridine-associated bleeding using multiple electrode whole-blood aggregometry. *Ann Thorac Surg* 2011;**92**:778–9	A
Gavrilov AO, Shilov AM. [Characteristics of the thromboelastogram indices of the arterial and venous blood acute myocardial infarct.] *Probl Gematol Pereliv Krovi* 1979;**24**:27–9	C, D
Gawaz M, Seyfarth M, Muller I, Rudiger S, Pogatsa-Murray G, Wolf B, *et al.* Comparison of effects of clopidogrel versus ticlopidine on platelet function in patients undergoing coronary stent placement. *Am J Cardiol* 2009;**87**:332–6	C, D
Geara AS, Azzi N, Bassil C, El-Sayegh S. Aspirin resistance in hemodialysis patients. *Int Urol Nephrol* 2012;**44**:323–5	D
Geisler T, Anders N, Paterok M, Langer H, Stellos K, Lindemann S, *et al.* Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007;**30**:372–4	C, D
Geisler T, Gawaz M, Steinhubl SR, Bhatt DL, Storey RF, Flather M. Current strategies in antiplatelet therapy – does identification of risk and adjustment of therapy contribute to more effective, personalized medicine in cardiovascular disease? *Pharmacol Ther* 2010;**127**:95–107. [Erratum published in *Pharmacol Ther* 2010;**128**:385]	A
Geisler T, Gawaz M. Editorial on 'Residual platelet reactivity is an independent predictor of myocardial injury in acute myocardial infarction patients on antiaggregant therapy' by Marcucci, *et al. Thromb Haemost* 2007;**98**:705–6	A
Geisler T, Grass D, Bigalke B, Stellos K, Drosch T, Dietz K, *et al.* The Residual Platelet Aggregation after Deployment of Intracoronary Stent (PREDICT) score. *J Thromb Haemost* 2008;**6**:54–61	C
Geisler T, Htun P, Fateh-Moghadam S, Bischofs C, Mueller K, Bigalke B, *et al.* Responsiveness to clopidogrel adversely influences outcome in patients with chronic kidney disease undergoing coronary interventions. *Eur Heart J* 2010;**31**:341	C
Geisler T, Kapp M, Gohring-Frischholz K, Daub K, Dosch C, Bigalke B, *et al.* Residual platelet activity is increased in clopidogrel- and ASA-treated patients with coronary stenting for acute coronary syndromes compared with stable coronary artery disease. *Heart* 2008;**94**:743–7	D
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Geisler T, Zurn C, Paterok M, Gohring-Frischholz K, Bigalke B, Stellos K, *et al.* Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Eur Heart J* 2008;**29**:1635–43	C
Geisler T, Zurn C, Simonenko R, Rapin M, Kraibooj H, Kilias A, *et al.* Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. *Eur Heart J* 2010;**31**:59–66	C

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Article	Reason for exclusion
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Gibbings G. No easy way to identify aspirin resistance. *Practitioner* 2008;**252**:6	A
Gibson CM, Ly HQ, Murphy SA, Ciaglo LN, Southard MC, Stein EB, *et al.* Usefulness of clopidogrel in abolishing the increased risk of reinfarction associated with higher platelet counts in patients with ST-elevation myocardial infarction (results from CLARITY-TIMI 28). *Am J Cardiol* 2006;**98**:761–3	A
Giugliano RP, McCabe CH, Sequeira RF, Frey MJ, Henry TD, Piana RN, *et al.* First report of an intravenous and oral glycoprotein IIb/IIIa inhibitor (RPR 109891) in patients with recent acute coronary syndromes: results of the TIMI 15A and 15B trials. *Am Heart J* 2000;**140**:81–93	C
Giusti B, Gori AM, Marcucci R, Saracini C, Sestini I, Paniccia R, *et al.* Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. *Am J Cardiol* 2009;**103**:806–11	C
Giusti B, Saracini C, Vestrini A, Magi A, Marcucci R, Rossi L, *et al.* Genetic variants besides CYP2C19*2 polymorphism are associated with major adverse cardiovascular events in high risk vascular patients on dual antiplatelet therapy. *Eur Heart J* 2010;**31**:156	C
Glauser J, Emerman CL, Bhatt DL, Peacock WF. Platelet aspirin resistance in ED patients with suspected acute coronary syndrome. *Am J Emerg Med* 2010;**28**:440–4	B
Gluszek J, Posadzy-Malaczynska A, Tykarski A, Pupek-Musialik D, Gracz M, Kara-Perz H. Acetylsalicylic acid (aspirin) test for the diagnosis of renovascular hypertension. *Clin Invest Med* 1997;**20**:171–5	D
Golanski J, Chizynski K, Golanski R, Watala C. [Application of platelet function analyzer (PFA-100™) and whole blood aggregometry to monitor blood platelet sensitivity to acetylsalicylic acid (aspirin). Is it possible to reliably monitor antiplatelet treatment using routine laboratory diagnostic methods?] *Pol Arch Med Wew* 2000;**104**:355–61	D
Goodman T, Ferro A, Sharma P. Pharmacogenetics of aspirin resistance: a comprehensive systematic review. *Br J Clin Pharmacol* 2008;**66**:222–32	D
Gordon B, Biss T, Butt T, McDiarmid A, Oezalp F, Pillay T, *et al.* Platelet mapping thromboelastography for individualized antiplatelet treatment after implantation of the HeartWare ventricular assist device. *J Heart Lung Transplant* 2011;**30**(Suppl. 1):S208–9	D
Gorog DA, Douglas H, Ahmed N, Lefroy DC, Davies GJ. Coronary angioplasty enhances platelet reactivity through von Willebrand factor release. *Heart* 2003;**89**:329–30	B, D
Gratsianskii NA. [Antiplatelet therapy in coronary heart disease. Some problems and achievements.] *Kardiologiia* 2010;**50**:4–21	A
Gray EN, Cheema FH. Letter to the editor. *ASAIO J* 2008;**54**:138	A
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Greenbaum AB, Grines CL, Bittl JA, Becker RC, Kereiakes DJ, Gilchrist IC, *et al.* Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. *Am Heart J* 2006;**151**:689	C
Greer DM. Aspirin and antiplatelet agent resistance: implications for prevention of secondary stroke. *CNS Drugs* 2010;**24**:1027–40	A
Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Comparison of methods to evaluate aspirin-mediated platelet inhibition after percutaneous intervention with stent implantation. *Platelets* 2011;**22**:188–95	D
Gritsiuk AI, Sopina NV. [Blood coagulation and fibrinolytic system in patients with marked coronary arteriosclerosis.] *Kardiologiia* 1970;**10**:9–16	C, D
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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
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Grove EL, Hvas AM, Kristensen SD. Aspirin resistance: myth or major problem? *Scand J Clin Lab Invest* 2008;**68**:257–9	A
Grove EL, Hvas AM, Kristensen SD. Platelet function testing in atherothrombotic disease: steps forward in managing resistance to antiplatelet therapy. *Kardiol Pol* 2008;**66**:478–9	A
Grundmann K, Jaschonek K, Kleine B, Dichgans J, Topka H. Aspirin non-responder status in patients with recurrent cerebral ischemic attacks. *J Neurol* 2003;**250**:63–6	D
Guan SY, Han YL, Li Y, Guo L, Yang BS, Wang SL, *et al.* [Effects of intensive antiplatelet therapy for patients with high on-treatment platelet reactivity after coronary stent implantation.] *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih* 2012;**40**:25–9	C
Guha S, Mookerjee S, Guha P, Sardar P, Deb S, Roy PD, *et al.* Antiplatelet drug resistance in patients with recurrent acute coronary syndrome undergoing conservative management. *Indian Heart J* 2009;**61**:348–52	D
Gupta MC, Dhamija JP, Mathur DS, Sharma BM. Role of propranolol and aspirin in decreasing platelet aggregation in occlusive cerebrovascular diseases. *J Assoc Physicians India* 1983;**31**:565–7	D
Gupta S, Gupta MM. Aspirin and clopidogrel resistance – a myth or reality: an update. *Indian Heart J* 2008;**60**:245–53	A
Gupta S, Gupta VK, Dhamija RK, Kela AK. Platelet aggregation patterns in normotensive and hypertensive subjects. *Indian J Physiol Pharmacol* 2002;**46**:379–82	B
Gupta S. When aspirin doesn't work. *Time* 2002;**159**:83	A
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Gurbel P. Aspirin – Scope and limitations. *Br J Cardiol* 2010;**17**(Suppl. 1):S8–9	A
Gurbel PA, Antonino MJ, Bliden KP, Dichiara J, Suarez TA, Singla A, *et al.* Platelet reactivity to adenosine diphosphate and long-term ischemic event. *J Thromb Haemost* 2009;**7**:572	C
Gurbel PA, Bilden KP, Tantry US. Diagnostics for aspirin resistance. *Mol Diagn Ther* 2008;**12**:55–6	A
Gurbel PA, Bliden KP, Antonino MJ, Gesheff T, Cummings CC, Dubois BV, *et al.* Time dependence of clopidogrel loading effect: platelet activation versus platelet aggregation. *Thromb Res* 2012;**129**:1–2	C
Gurbel PA, Bliden KP, Guyer K, Cho PW, Zaman KA, Kreutz RP, *et al.* Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. *J Am Coll Cardiol* 2005;**46**:1820–6	C
Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;**107**:2908–13	C
Gurbel PA, Bliden KP, Kreutz RP, Dichiara J, Antonino MJ, Tantry US. The link between heightened thrombogenicity and inflammation: pre-procedure characterization of the patient at high risk for recurrent events after stenting. *Platelets* 2009;**20**:97–104	C
Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissha MZ, *et al.* Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005;**46**:1827–32	D
Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation* 2005;**111**:1153–9	C
Gurbel PA, Bliden KP. Durability of platelet inhibition by clopidogrel. *Am J Cardiol* 2003;**91**:1123–5	C
Gurbel PA, Jeong Y-H, Mahla E, Bliden K, Tantry U. The association of preoperative platelet function testing and bleeding in patients undergoing elective coronary artery bypass grafting. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E1455	B, D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Gurbel PA, Mahla E, Antonino MJ, Tantry US. Response variability and the role of platelet function testing. *J Invasive Cardiol* 2009;**21**:172–8	A
Gurbel PA, Mahla E, Tantry US. Peri-operative platelet function testing: the potential for reducing ischaemic and bleeding risks. *Thromb Haemost* 2011;**106**:248–52	A
Gurbel PA, Tantry US. Platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents? *Circulation* 2012;**125**:1276–87	A
Gurbel PA, Tantry US, Shuldiner AR. The worry about clopidogrel 'nonresponsiveness': identification and treatment in the post-percutaneous coronary intervention patient. *JACC Cardiovasc Interv* 2009;**2**:1102–4	A
Gurbel PA, Tantry US. Acceptance of high platelet reactivity as a risk factor: now, what do we do about it? *JACC Cardiovasc Interv* 2010;**3**:1008–10	A
Gurbel PA, Tantry US. An initial experiment with personalized antiplatelet therapy: the GRAVITAS trial. *JAMA* 2011;**305**:1136–7	A
Gurbel PA, Tantry US. Antiplatelet resistance – fact or myth? *Am Heart Hosp J* 2009;**7**:50–7	A
Guthikonda S, Kleiman NS. Is aspirin resistance valid? *Future Cardiol* 2006;**2**:1–4	A
Ha SJ, Woo JS, Kim WS, Kim SJ, Kim W, Kim MK, *et al.* The effect of cilostazol adding or clopidogrel doubling on platelet function with diabetes mellitus and coronary artery disease on dual antiplatelet therapy. *Eur Heart J* 2010;**31**:975	C, D
Hackeng CM, Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJT, *et al.* Prospective comparison of platelet function tests in predicting clinical outcome in 1069 patients undergoing coronary stent implantation: the popular study. *Pathophysiol Haemost Thromb* 2010;**37**:A129	C
Halushka MK, Halushka PV. Why are some individuals resistant to the cardioprotective effects of aspirin? Could it be thromboxane A2? *Circulation* 2002;**105**:1620–2	A
Hankey GJ, Eikelboom JW. Aspirin resistance. *BMJ* 2004;**328**:477–9	A
Harding S, Johnston L, Michel J, Ramanathan A, La FA, Sasse A, *et al.* High on treatment platelet reactivity is common and differs among ethnic groups. *Heart Lung Circul* 2011;**20**:S34–5	D
Harmsze AM, van Werkum JW, Hackeng CM, Ruven HJ, Kelder JC, Bouman HJ, *et al.* The influence of CYP2C19*2 and *17 on on-treatment platelet reactivity and bleeding events in patients undergoing elective coronary stenting. *Pharmacogenet Genomics* 2012;**22**:169–75	C
Harmsze AM, van Werkum JW, Souverein PC, Breet NJ, Bouman HJ, Hackeng CM, *et al.* Combined influence of proton-pump inhibitors, calcium-channel blockers and CYP2C19*2 on on-treatment platelet reactivity and on the occurrence of atherothrombotic events after percutaneous coronary intervention. *J Thromb Haemost* 2011;**9**:1892–901	C
Harmsze AM, van Werkum JW, ten Berg JM, Ruven HJT, Hackeng CM, Tjoeng MM, *et al.* Effect of genetic variants on the effectiveness of clopidogrel. *Pharm Weekbl* 2011;**146**:79–84	B, C
Harrison P, Keeling D. Platelet hyperactivity and risk of recurrent thrombosis. *J Thromb Haemost* 2006;**4**:2544–6	A
Harrison P, Mumford A. *Screening Tests of Platelet Function: Update on their Appropriate Uses for Diagnostic Testing*. New York, NY: Thieme; 2009	A
Harrison P. The influence of citrate concentrations on PFA-100 closure times, platelet hyper-reactivity and aspirin monitoring. *Thromb Res* 2010;**126**:e137–8	D
Hennekens CH, Schror K, Weisman S, FitzGerald GA. Terms and conditions: semantic complexity and aspirin resistance. *Circulation* 2004;**110**:1706–8	A
Henry P, Drouet L. Resistances to antiplatelet agents. *Arch Mal Coeur Vaiss Prat* 2010;**16**:14–21	A
Hezard N, Tessier-Marteau A, Macchi L. New insight in antiplatelet therapy monitoring in cardiovascular patients: from aspirin to thienopyridine. *Cardiovasc Hematol Disord Drug Targets* 2010;**10**:224–33	A
Hillarp A, Lethagen S, Mattiasson I. Aspirin resistance is not a common biochemical phenotype explained by unblocked cyclooxygenase-1 activity. *J Thromb Haemost* 2003;**1**:196–7	A

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Hillegass WB, Zoghbi G, Brott BC, Kilgore ML, Chapman GD, Misra VK. Cost-effectiveness of new oral antiplatelet agents and testing strategies during early invasive management of acute coronary syndrome patients. *Circulation* 2011;**124**(Suppl. 1):A18228	B
Hillman RS. Platelet aspirin resistance detection and validation. *J Am Coll Cardiol* 2006;**47**:2565	A
Hjemdahl P. Platelet reactivity, exercise, and stable coronary artery disease. *Eur Heart J* 1995;**16**:1017–19	A
Hjemdahl P. Should we monitor platelet function during antiplatelet therapy? *Heart* 2008;**94**:685–7	A
Ho WK, Hankey GJ, Eikelboom JW. Is there a role for laboratory testing to identify patients at risk of aspirin treatment failure? *Blood Coagul Fibrinolysis* 2004;**15**:129–30	A
Hobikoglu GF, Norgaz T, Aksu H, Ozer O, Erturk M, Nurkalem Z, *et al.* High frequency of aspirin resistance in patients with acute coronary syndrome. *Tohoku J Exp Med* 2005;**207**:59–64	D
Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, *et al.* Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006;**48**:1742–50	C
Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, *et al.* Time dependence of platelet inhibition after a 600 mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005;**111**:2560–4	C
Hodges JS. Incorrect p value in: comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 2010;**303**:1257	A
Hoffmann S. Do platelet function assays predict clinical outcomes in clopidogrel pretreated patients undergoing elective PCI? *Herz* 2010;**35**:50	A
Hokimoto S, Mizobe M, Chitose T, Kaikita K, Nakagawa K, Ogawa H. Impact of CYP2C19 polymorphism and diabetes mellitus on platelet reactivity and clinical outcomes in patients following coronary stent placement. *Circulation* 2011;**124**(Suppl. 1):A15054	B, C
Hokimoto S, Ogawa H. Is it safe to use a proton pump inhibitor with clopidogrel? A comparison of clopidogrel with or without rabeprazole in Japan. *Gastroenterology* 2010;**138**(Suppl. 1):S498	C
Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA* 2011;**306**:2704–14	B, C
Hong DM, Jeon YS, Kim JH, Lim TW, Lim YJ, Bahk JH, *et al.* Preoperative platelet response to collagen is associated with myocardial injury after off-pump coronary bypass graft in patients taking aspirin. *Korean J Anesth* 2010;**58**:129–35	D
Hong JM, Shin DH, Lee JS. Comparison of platelet aggregation with thienopyridines in acute cerebral ischemia. *Cerebrovasc Dis* 2011;**31**:262–3	B
Horiuchi H, Ikeda T, Taniguchi R, Kita T, Kimura T, Hisanori H. Characterization of the antiplatelet effect of aspirin at enrollment and after a 2-year follow-up in the real clinical setting in Japan. *J Mol Cell Cardiol* 2010;**48**(Suppl. 1):S115	D
Houel R, Mazoyer E, Kirsch M, Boval B, Drouet L, Loisance DY. Resistance to aspirin after external ventricular assist device implantation. *J Thorac Cardiovasc Surg* 2003;**126**:1636–7	D
Hovens MM, Snoep JD, Eikenboom JC, Van Der Bom JG, Mertens BJ, Huisman MV. Prevalence of persistent platelet reactivity despite use of aspirin: a systematic review. *Am Heart J* 2007;**153**:175–81	D
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Huang Y, Gueyffier F, Boissel JP, Nony P. Can poor-compliance be considered as an important cause for aspirin resistance? An 'in-silico' approach. *Fundam Clin Pharmacol* 2010;**24**:62	A
Huczek Z, Filipiak KJ, Kochman J, Michalak M, Roik M, Grabowski M, *et al.* Medium on-treatment platelet reactivity to ADP is favorable in patients with acute coronary syndromes undergoing coronary stenting. *Platelets* 2011;**22**:521–9	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Huczek Z, Filipiak KJ, Kochman J, Michalak M, Roik M, Opolski G. Variable response in platelet reactivity to 600 mg clopidogrel-loading dose influences prognosis in ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2009;**53**:A428	B, C
Huczek Z, Filipiak KJ, Kochman J, Piatkowski R, Grabowski M, Roik M, *et al.* Baseline platelet reactivity in acute myocardial infarction treated with primary angioplasty – influence on myocardial reperfusion, left ventricular performance, and clinical events. *Am Heart J* 2007;**154**:62–70	C
Huczek Z, Filipiak KJ, Kochman J, Piatkowski R, Grabowski M, Roik M, *et al.* Prognostic significance of platelet function in the early phase of ST-elevation myocardial infarction treated with primary angioplasty. *Med Sci Monit* 2008;**14**:CR144–51	C
Hulot J-S, Collet J-P, Cayla G, Silvain J, Allanic F, Bellemain-Appaix A, *et al.* CYP2C19 but not PON1 genetic variants influence clopidogrel pharmacokinetics, pharmacodynamics, and clinical efficacy in post-myocardial infarction patients. *Circ Cardiovasc Interv* 2011;**4**:422–8	C
Husstedt IW, Grotemeyer KH, Evers S, Staschewski F, Wertelewski R. Progression of distal symmetric polyneuropathy during diabetes mellitus: clinical, neurophysiological, haemorheological changes and self-rating scales of patients. *Eur Neurol* 1997;**37**:90–4	D
Ibrahim K. Increased rate of stent thrombosis due to clopidogrel resistance in patients in therapeutic hypothermia after sudden cardiac death. *Eur Heart J* 2011;**32**:252	C
Iijima R, Ndrepepa G, Mehilli J, Bruskina O, Schulz S, Schomig A, *et al.* Relationship between platelet count and 30-day clinical outcomes after percutaneous coronary interventions. Pooled analysis of four ISAR trials. *Thromb Haemost* 2007;**98**:852–7	C
Ikeda T, Taniguchi R, Watanabe S, Kawato M, Kondo H, Shirakawa R, *et al.* Characterization of the antiplatelet effect of aspirin at enrollment and after 2-year follow-up in a real clinical setting in Japan. *Circ J* 2010;**74**:1227–35	D
Inoue Y, Shimizu M, Hasuda T, Uehara Y, Nakae S, Kubota T, *et al.* Effect of platelet aggregation inhibition by aspirin and clopidogrel in post stenting patients. *J Mol Cell Cardiol* 2010;**48**(Suppl. 1):S173	D
Isbir S, Ak K, Aksoy N. Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting. *Eur J Cardiothorac Surg* 2005;**28**:514–15	A
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it-Mokhtar O, Bonello L, Benamara S, Paganelli F. High on treatment platelet reactivity. *Heart Lung Circ* 2012;**21**:12–21	A
Itoh T, Nakai K, Ono M, Hiramori K. Can the risk for acute cardiac events in acute coronary syndrome be indicated by platelet membrane activation marker P-selectin? *Coron Artery Dis* 1995;**6**:645–50	B
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Ivanova NA. [Some indices of the blood coagulation system and thrombus-formation in patients with diabetes mellitus.] *Kardiologiia* 1971;**11**:121–5	C, D
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Jaremo P, Milovanovic M, Lindahl TL, Richter A. Elevated platelet density and enhanced platelet reactivity in stable angina pectoris complicated by diabetes mellitus type II. *Thromb Res* 2009;**124**:373–4	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Jeon HW, Cha JK. Factors related to progression of middle cerebral artery stenosis determined using transcranial Doppler ultrasonography. *J Thromb Thrombolysis* 2008;**25**:265–9	D
Jeon SB, Song HS, Kim BJ, Kim HJ, Kang DW, Kim JS, *et al.* Biochemical aspirin resistance and recurrent lesions in patients with acute ischemic stroke. *Eur Neurol* 2010;**64**:51–7	D
Jeong YH, Hwang JY, Kim IS, Park Y, Hwang SJ, Lee SW, *et al.* Adding cilostazol to dual antiplatelet therapy achieves greater platelet inhibition than high maintenance dose clopidogrel in patients with acute myocardial infarction: results of the adjunctive cilostazol versus high maintenance dose clopidogrel in patients with AMI (ACCEL-AMI) study. *Circ Cardiovasc Interv* 2010;**3**:17–26	C, D
Jeong Y-H, Hwang S-J, Park Y, Kim I-S, Kwak CH, Hwang J-Y. Cytochrome 2C19 polymorphism and response to adjunctive cilostazol versus high maintenance-dose clopidogrel in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A130	C, D
Jeong Y-H, Kim I-S, Choi B-R, Kwak CH, Hwang J-Y. The optimal threshold of high post-treatment platelet reactivity could be defined by a point-of-care VerifyNow P2Y12 assay. *Eur Heart J* 2008;**29**:2186–7	C
Jeong Y-H, Kim I-S, Park Y, Yun S-E. Platelet inhibition by adjunctive cilostazol vs. high maintenance-dose clopidogrel in patients with acute myocardial infarction according to cytochrome P450 2C19 genotype. *J Thromb Haemost* 2011;**9**:48–9	D
Jeong Y-H, Koh J-S, Kwon TJ, Park Y, Kim I-S. Impact of the cytochrome P450 2C19*3 polymorphism on platelet reactivity and adverse clinical events in patients with acute myocardial infarction. *J Thromb Haemost* 2011;**9**:793	B, C
Jeong Y-H, Kwon TJ, Tantry US, Park Y, Hwang S-J, Bliden KP, *et al.* Correlation between platelet reactivity and type of post-discharge bleeding events in PCI-treated patients: results of the ACCEL-BLEED study. *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B221	B, C
Jeong Y-H, Lee K, Yoo S-Y, Park J-H, Suh J, Park K-H. Accelerated inhibition of platelet aggregation, inflammation and myonecrosis by adjunctive cilostazol loading in patients with acute coronary syndrome: the results of the ACCEL-LOADING-ACS multicenter randomized trial. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E455	C
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Jeong YH, Tantry US, Bliden KP, Gurbel PA. Cilostazol to overcome high on-treatment platelet reactivity in Korean patients treated with clopidogrel and calcium-channel blocker. *Circ J* 2011;**75**:2534–6	A
Jeong YH, Tantry US, Kim IS, Koh JS, Kwon TJ, Park Y, *et al.* Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin. *Circ Cardiovasc Interv* 2011;**4**:585–94	C
Jeong YH, Tantry UT, Jung TJ, Park YH, Kim IS, Bliden KA, *et al.* Impact of the cytochrome P450 2C19*3 polymorphism on platelet reactivity and adverse clinical events in patients with acute myocardial infarction. *Eur Heart J* 2011;**32**:508	C
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Jian C, Lin L, Li F. Prevalence and risk factors for aspirin resistance in older patients with cardiovascular disease. *Heart* 2011;**97**(Suppl. 3):A101	D
Jilma B, Fuchs I. Aspirin. Methods to assess aspirin resistance. *J Thromb Haemost* 2004;**2**:337–8	A
Jilma B, Fuchs I. Detecting aspirin resistance with the platelet function analyzer (PFA-100). *Am J Cardiol* 2001;**88**:1348–9	A

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Article	Reason for exclusion
Jilma B. Synergistic antiplatelet effects of clopidogrel and aspirin detected with the PFA-100 in stroke patients. *Stroke* 2003;**34**:849–54	A
Jilma B. Therapeutic failure or resistance to aspirin. *J Am Coll Cardiol* 2004;**43**:1332–3	A
Johns A, Fisher M, Knappertz V. Aspirin and clopidogrel resistance: an emerging clinical entity. *Eur Heart J* 2006;**27**:1754–5	A
Johnson GJ, Sharda AV, Rao GH, Ereth MH, Laxson DD, Owen WG. Measurement of shear-activated platelet aggregate formation in non-anticoagulated blood: utility in detection of clopidogrel-aspirin-induced platelet dysfunction. *Clin Appl Thromb Hemost* 2012;**18**:140–9	D
Jukema JW, Collet J-P, De Luca L. Antiplatelet therapy in patients with ST-elevation myocardial infarction undergoing myocardial revascularisation: beyond clopidogrel. *Curr Med Res Opin* 2012;**28**:203–11	C
Jungmayr P. Cardiovascular morbidity: clinical relevance of aspirin resistance. *Dtsch Apoth Ztg* 2008;**148**:43–4	A
Kabbani SS, Watkins MW, Ashikaga T, Terrien EF, Holoch PA, Sobel BE, *et al.* Platelet reactivity characterized prospectively: a determinant of outcome 90 days after percutaneous coronary intervention. *Circulation* 2001;**104**:181–6	C
Kabbani SS, Watkins MW, Ashikaga T, Terrien EF, Sobel BE, Schneider DJ. Usefulness of platelet reactivity before percutaneous coronary intervention in determining cardiac risk one year later. *Am J Cardiol* 2003;**91**:876–8	C
Kakouros N, Kickler TS, Laws K, Rade JJ. Hematocrit significantly affects the results of the verifynow assay in patients receiving dual antiplatelet therapy. *Circulation* 2011;**124**(Suppl. 1):A17082	D
Kakuliia MS, Panchenko VM. [Functional status of thrombocytes in patients with acute forms of ischemic heart disease.] *Klin Med (Mosk)* 1987;**65**:88–92	B, C, D
Kalyanasundaram A, Berger PB. Routine platelet testing should not be performed on all patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2010;**3**:284–7	A
Kang HS, Kwon BJ, Kim JE, Han MH. Preinterventional clopidogrel response variability for coil embolization of intracranial aneurysms: clinical implications. *Am J Neuroradiol* 2010;**31**:1206–10	C
Kapoor JR. Enteric coating is a possible cause of aspirin resistance. *J Am Coll Cardiol* 2008;**52**:1276–7	A
Karabulut H, Toraman F, Evrenkaya S, Goksel O, Tarcan S, Alhan C. Clopidogrel does not increase bleeding and allogenic blood transfusion in coronary artery surgery. *Eur J Cardiothorac Surg* 2004;**25**:419–23	C
Kasotakis G, Pipinos II, Lynch TG. Current evidence and clinical implications of aspirin resistance. *J Vasc Surg* 2009;**50**:1500–10	A
Kaymaz C, Tanboga IH, Tokgoz HC, Poci N, Can MM, Kirca N, *et al.* Clinical, procedural, cardiometabolic and laboratory correlates of platelet reactivity to clopidogrel and aspirin on multiplate analyser in patients with coronary stenting. *Eur Heart J* 2011;**32**:752–3	D
Kerenyi A, Soltesz P, Veres K, Szegedi G, Muszbek L. Monitoring platelet function by PFA-100 closure time measurements during thrombolytic therapy of patients with myocardial infarction. *Thromb Res* 2005;**116**:139–44	D
Kim C-H, Park K-W, Jeon K, Kang S-H, Kim K-H, Lee H-Y, *et al.* Decreased response to clopidogrel is a risk factor for cardiovascular events after stent implantation: Cross verify study. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A51	C
Kim H-L, Suh J-W, Lee S-P, Oh I-Y, Kang H-J, Koo B-K, *et al.* No legacy effect of six months' treatment of cilostazol on the long-term prognosis of patients who underwent drug-eluting stent implantation: 2-year follow-up of the cilon-t trial. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E1404	C
Kim IS, Choi BR, Jeong YH, Kwak CH, Kim S. The CYP2C19*2 and CYP2C19*3 polymorphisms are associated with high post-treatment platelet reactivity in Asian patients with acute coronary syndrome. *J Thromb Haemost* 2009;**7**:897–9	B, C, D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Kim IS, Jeong YH, Kang MK, Koh JS, Park Y, Hwang SJ, *et al.* Correlation of high post-treatment platelet reactivity assessed by light transmittance aggregometry and the VerifyNow P2Y12 assay. *J Thromb Thrombolysis* 2010;**30**:486–95	C
Kim J-Y, Yoon J. Aspirin and clopidogrel resistance in drug eluting stent era. *Korean Circ J* 2007;**37**:135–47	A
Kim KE, Woo KS, Goh RY, Quan ML, Cha KS, Kim MH, *et al.* Comparison of laboratory detection methods of aspirin resistance in coronary artery disease patients. *Int J Lab Hematol* 2010;**32**:50–5	D
Kim MH, Yu LH, Kim JH, Park SY, Park TH, Cha KS, *et al.* Initial loading therapy of cilostazol improved antiplatelet responsiveness in patient with percutaneous coronary intervention. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A208	D
King A, Bath PM, Markus HS. Clopidogrel versus dipyridamole in addition to aspirin in reducing embolization detected with ambulatory transcranial Doppler: a randomized trial. *Stroke* 2011;**42**:650–5	C
King A, Bath PMW, Markus H. What is the best antiplatelet regimen in acute carotid stenosis? A randomised trial comparing clopidogrel versus dipyridamole in addition to aspirin on asymptomatic embolisation. *Cerebrovasc Dis* 2010;**29**:160–1	C
Kirtane AJ, Parise H, Witzenbichler B, Weisz G, Rinaldi M, Neumann F-J, *et al.* Does platelet function testing add significant incremental risk stratification to unselected patients undergoing des implantation? The adapt-des study. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E292	C
Kirtane AJ, Rinaldi M, Parise H, Witzenbichler B, Weisz G, Neumann F-J, *et al.* Impact of point-of-care platelet function testing among patients with and without acute coronary syndromes undergoing PCI with drug-eluting stents: An ADAPT-des substudy. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E291	C
Kirtane AJ, Stuckey T, Parise H, Witzenbichler B, Weisz G, Rinaldi M, *et al.* Impact of point-of-care platelet function testing among diabetic and non-diabetic patients undergoing PCI with drug-eluting stents: an adapt-des substudy. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E268	B
Kleiman NS. Could clopidogrel's platelet inhibition be enhanced by an increased loading dose and eptifibatide? *Nat Clin Pract Cardiovasc Med* 2005;**2**:344–5	A
Kliger C, Babaev A, Shah B, Feit F, Slater J, Attubato M. Dual antiplatelet therapy responsiveness in patients undergoing percutaneous revascularization for peripheral arterial occlusive disease. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E2049	D
Kobune K, Inoue M, Morikawa M, Tsuboi M, Takanami Y, Iwane Y, *et al.* Effects of combination therapy with low-dose aspirin and warfarin on platelet functions after heart valve replacement. *Res Comm Chem Pathol Pharmacol* 1991;**74**:153–65	D
Koerner H, Derveaux C, Alexandrou M, Graeber S, Roth C, Papanagiotou P, *et al.* Do clopidogrel nonresponders have an increased risk of adverse events during supra-aortal angioplasty and stenting? *Stroke Res Treat* 2012;**2012**:904534	C
Konorza TFM. TAILORED: tailored clopidogrel loading doses according to platelet reactivity monitoring decrease early stent thrombosis. *Herz* 2009;**34**:74	C
Kooistra MP, van Es A, Marx JJ, Hertsig ML, Struyvenberg A. Low-dose aspirin does not prevent thrombovascular accidents in low-risk haemodialysis patients during treatment with recombinant human erythropoietin. *Nephrol Dial Transplant* 1994;**9**:1115–20	A
Koscielny J, Aslan T, Meyer O, Kiesewetter H, Jung F, Mrowietz C, *et al.* Use of the platelet reactivity index by Grotemeyer, platelet function analyzer, and retention test Homburg to monitor therapy with antiplatelet drugs. *Semin Thromb Hemost* 2005;**31**:464–9	B, D
Koscielny J, Meyer O, Kiesewetter H, Jung F, Latza R. [Platelet reactivity index by Grotemeyer.] *Hamostaseologie* 2004;**24**:207–10	A
Kottke BA. The ultimate solution to the problem of aspirin resistance. *J Am Coll Cardiol* 2008;**52**:1276	A
Koul S, Andell P, Martinsson A, Smith JG, Schersten F, Harnek J, *et al.* Upstream clopidogrel followed by pre-PCI prasugrel gives rapid platelet inhibition and represents a feasible option in STEMI patients undergoing primary PCI. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E526	C
Kour D, Tandon VR, Kapoor B, Mahajan A, Parihar A, Smotra S. Aspirin resistance. *JK Science* 2006;**8**:116–17	A

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Kralisz P, Dobrzycki S, Nowak K, Kochman W, Gajewska-Bachorzewska H, Gugala K, *et al.* Platelet inhibition by increased tirofiban dosing during primary coronary angioplasty for ST elevation myocardial infarction. *Kardiol Pol* 2004;**60**:459–67	C
Kramer MC, Nieuwland R, Sturk A, de Winter RJ. [Routine platelet aggregation inhibition not useful when using acetylsalicylic acid or clopidogrel.] *Ned Tijdschr Geneeskd* 2009;**153**:190–5	A
Kratzer MA. Platelet function analyzer (PFA)–100 closure time in the evaluation of platelet disorders and platelet function: a rebuttal. *J Thromb Haemost* 2006;**4**:1845–6	A
Kremneva LV, Shalaev SV. [Resistance to desaggregants: causes, clinical implication, methods of diagnosis and correction.] *Ter Arkh* 2008;**80**:89–95	A
Krishna V, Diamond GA, Kaul S. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents? The role of platelet reactivity and genotype testing in the prevention of atherothrombotic cardiovascular events remains unproven. *Circulation* 2012;**125**:1288–303	A
Kronish IM, Rieckmann N, Shimbo D, Davidson KW. Letter by Kronish, *et al.* regarding article, 'Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700-patient study of aspirin resistance'. *Circulation* 2007;**115**:e45	A
Kubik MM, Richardson SG. A serial study of platelet reactivity throughout the first six months after myocardial infarction: its modification by sulphinpyrazone. *Postgrad Med J* 1987;**63**:351–6	B
Kudaravalli J, Deshpande N, Avanapu SR, Vijaya LG, Nagaveni. Evaluation of aspirin resistance in elderly people in rural population in India. *Der Pharm Lett* 2011;**3**:5–9	D
Kuliczkowski W, Halawa B, Korolko B, Mazurek W. Aspirin resistance in ischaemic heart disease. *Kardiol Pol* 2005;**62**:14–25	D
Kusunoki M, Kimura K, Nagatsuka K, Isaka Y, Uyama O, Yoneda S, *et al.* Platelet hyperaggregability in ischemic cerebrovascular disease and effects of aspirin. *Thromb Haemost* 1982;**48**:117–19	D
Kuzniatsova N, Shantsila E, Blann AD, Tse HF, Lip GYH. Is increased arterial stiffness related to aspirin responsiveness in patients with coronary artery disease: a possible mechanism for increased cardiovascular events in aspirin non-responders? *Eur Heart J* 2011;**32**:253	D
Kwok CS, Loke YK. Critical overview on the benefits and harms of aspirin. *Pharmaceuticals* 2010;**3**:1491–506	C
Kwon SU, Lee J-H, Cha J-K, Lee SJ, Ha S-W. Addition of cilostazol reduce biochemical aspirin resistance in aspirin users with ischemic stroke. *Stroke* 2009;**40**:e270	D
Lakkis N, Dokainish H, Abuzahra M, Tsyboulev V, Jorgensen J, De Leon AP, *et al.* Reticulated platelets in acute coronary syndrome: a marker of platelet activity. *J Am Coll Cardiol* 2004;**44**:2091–3	A, C, D
Lam H, Chan CK, Yip SF, Yam PW, Chui KL, Chan YH, *et al.* Monocyte platelet aggregate act as platelet function assay and prognostic marker for acute myocardial infarction. *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B95	C
Lam W, Gill JB, Trask RV, Mallavarapu CT, Rocha-Singh KJ, Mikell FL, *et al.* Comparative 30-day economic and clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor use during elective percutaneous coronary intervention: Prairie ReoPro Versus Integrilin Cost Evaluation (PRICE) trial. *Am Heart J* 2001;**141**:402–9	C
Lancaster G. Aspirin resistance, an emerging, often overlooked, factor in the management of patients with coronary artery disease. *Clin Cardiol* 2006;**29**:334	A
Lanza GA, Scalone G, Battipaglia I, Barone L, Coviello I, Milo M, *et al.* Evidence of increased platelet reactivity in the first six months after acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1093	C
Lassar TA, Simon DI, Croce K. Optimizing antiplatelet therapy following percutaneous coronary intervention: clinical pathways for platelet function testing. *Rev Cardiovasc Med* 2011;**12**(Suppl. 1):S23–33	A
Latour JG, Theroux P, Bourassa MG. Sulfinpyrazone decreases epinephrine-induced platelet aggregation after myocardial infarction. *Am J Cardiol* 1982;**50**:938–44	B

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Lee K, Lee S-W, Lee J-W, Kim S-Y, Youn Y-J, Ahn M-S, *et al.* The significance of clopidogrel low-responsiveness on stent thrombosis and cardiac death assessed by the VerifyNow P2Y12 assay in patients with acute coronary syndrome within 6 months after drug-eluting stent implantation. *Korean Circ J* 2009;**39**:512–18	C
Lee KH, Lee SH, Lee JW, Sung JK, Wang HS, Youn YJ, *et al.* The significance of clopidogrel low-responsiveness assessed by a point-of-care assay in acute coronary syndrome patients undergoing coronary stenting. *Eur Heart J* 2009;**30**:328	C
Lee SJ, Kim JG, Ko Y, Lee BH. Clopidogrel-induced platelet inhibition may predict early ischemic complications following stent-assisted angioplasty for symptomatic cerebral atherosclerotic disease. *Stroke* 2011;**42**:e96	C
Lee SP, Bae JW, Park KW, Rha SW, Bae JH, Suh JW, *et al.* Inhibitory interaction between calcium channel blocker and clopidogrel. Efficacy of cilostazol to overcome it. *Circ J* 2011;**75**:2581–9	C
Lee S-P, Suh J-W, Park KW, Lee H-Y, Kang H-J, Koo B-K, *et al.* Study design and rationale of 'Influence of Cilostazol-based triple anti-platelet therapy on ischemic complication after drug-eluting stent implantation (CILON-T)' study: a multicenter randomized trial evaluating the efficacy of Cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease. *Trials* 2010;**11**:87	A
Legrand V, Barbato E, Chenu P, Wijns W. Platelet reactivity after ASA and clopidogrel treatment assessed with VerifyNow point-of-care analysis in patients with stable coronary artery disease undergoing percutaneous coronary intervention. *Eurointervention* 2010;**6**(Suppl. H):12	D
Lemesle G, Mokhtar OA, Armero S, Mancini J, Bonello C, Tahirou I, *et al.* Relationship between platelet reactivity inhibition and major bleeding in patients undergoing percutaneous coronary intervention. *Cardiovasc Revasc Med* 2010;**11**:207	C
Leone G, Valori VM, Sandric S, Cudillo L, Bizzi B. Platelet activation and thromboembolism in patients with mitral valve prolapse. *Thromb Res* 1982;**28**:831–5	D
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Li Y, Han Y, Wang S, Li C, Mai X, Jing Q, *et al.* Effects of laboratory test guided, individually tailored antiplatelet therapy after percutaneous coronary artery intervention. *Circulation* 2010;**122**:e67	C
Lian J, Azmi S, Navaratnam P. Gaps and unmet needs in antiplatelet therapies for acute coronary syndrome (ACS) and chronic coronary heart disease (CHD). *Value Health* 2011;**14**:A47	C
Lievykh AE, Mamchur VI, Rodionova VV, Bespala DV. Thiotriazolin enhances antiaggregatory activity of acetylsalicilic acid and reduces its gastrotoxicity in patients with coronary heart disease. *Basic Clin Pharmacol Toxicol* 2011;**109**:100	D
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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
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Loew D, Vinazzer H. Influence of simultaneous administration of low-dose heparin and acetylsalicylic acid on blood coagulation and platelet functions. *Haemostasis* 1974;**3**:319–28	B, D
Lordkipanidzé M, Pharand C, Diodati JG. Comparison of different methods of measurement of aspirin resistance: using the appropriate statistic (reply). *Eur Heart J* 2008;**29**:138–9	A
Lotrionte M, Biondi-Zoccai GG, Agostoni P, Sheiban I. Comparison of different methods of measurement of aspirin resistance: using the appropriate statistic. *Eur Heart J* 2008;**29**:138–9	A
Lu YL, Chen YD, Lu SZ. [Effects of intensive antiplatelet therapy in patients with high platelet aggregability after percutaneous coronary intervention.] *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih* 2007;**35**:793–6	C
Lutsep H. Update on selecting and adjusting antiplatelet therapy for prevention of noncardiogenic, recurrent ischemic stroke. *Exp Rev Cardiovasc Ther* 2011;**9**:1295–303	A
Luxembourg B, Mani H, Toennes SW, Strubel G, Klaeffling C, Daemgen-von Brevern G, *et al.* Factitious anticoagulant-resistance as a cause of recurrent arterial bypass graft occlusions. *Thromb Haemost* 2007;**97**:1046–8	A
Luzak B, Boncler M, Rywaniak J, Wilk R, Stanczyk L, Czyz M, *et al.* The effect of a platelet cholesterol modulation on the acetylsalicylic acid-mediated blood platelet inhibition in hypercholesterolemic patients. *Eur J Pharmacol* 2011;**658**:91–7	D
Luzak B, Boncler M, Rywaniak J, Wilk R, Stanczyk L, Rysz J, *et al.* The effect of platelet and plasma oxLDL and platelet cholesterol on the ASA-mediated blood platelet inhibition and platelet protein acetylation in atorvastatin-treated hypercholesterolemic patients. *J Thromb Haemost* 2009;**7**:349	D
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Madsen EH, Saw J, Kristensen SR, Schmidt EB, Pittendreigh C, Maurer-Spurej E. Long-term aspirin and clopidogrel response evaluated by light transmission aggregometry, VerifyNow, and thrombelastography in patients undergoing percutaneous coronary intervention. *Clin Chem* 2010;**56**:839–47	D
Madsen EH, Schmidt EB, Gehr N, Johannesen NL, Kristensen SR. Testing aspirin resistance using the Platelet Function Analyzer-100: some methodological caveats and considerations. *J Thromb Haemost* 2008;**6**:386–8	D
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Maiorov I. [The status of the blood anticoagulation system in angina pectoris and myocardial infarct.] *Kardiologiia* 1968;**8**:24–30	B
Malanowicz W. [A preliminary evaluation of thromboelastography in coronary heart diseases.] *Pol Arch Med Wewn* 1966;**36**:351–6	B, D
Malek LA, Bilinska ZT, Sitkiewicz D, Klopotowski M, Witkowski A, Ruzyllo W. Platelet reactivity on aspirin, clopidogrel and abciximab in patients with acute coronary syndromes and reduced estimated glomerular filtration rate. *Thromb Res* 2010;**125**:67–71	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
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Malek LA, Spiewak M, Filipiak KJ, Grabowski M, Szpotanska M, Rosiak M, *et al.* Persistent platelet activation is related to very early cardiovascular events in patients with acute coronary syndromes. *Kardiol Pol* 2007;**65**:40–5	D
Malmstrom RE, Ostergren J, Jorgensen L, Hjemdahl P, CASTOR investigators. Poor performance with a platelet counting technique to monitor clopidogrel inhibitory effects in the point-of-care setting. *Thromb Res* 2010;**125**:473–4	C, D
Mamelov I. [Thrombelastographic data in diseases of the peripheral vessels.] *Vestn Khir Im I I Grek* 1966;**97**:76–7	B, C
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Mangiacapra F, Barbato E. Individual variability of response to antiplatelet therapy is an important determinant of adverse clinical outcome. *High Blood Press Cardiovasc Prev* 2010;**17**:121–30	A
Mangiacapra F, Barbato E. Residual platelet reactivity: predicting short- and long-term clinical outcome in patients undergoing percutaneous coronary revascularization. *Biomarkers Med* 2010;**4**:421–34	A
Mangiacapra F, De Bruyne B, Muller O, Trana C, Ntalianis A, Bartunek J, *et al.* High residual platelet reactivity after clopidogrel: extent of coronary atherosclerosis and periprocedural myocardial infarction in patients with stable angina undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv* 2010;**3**:35–40	C
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Mangiacapra F, Patti G, Barbato E, Peace AJ, Ricottini E, Vizzi V, *et al.* A therapeutic window for platelet reactivity for patients undergoing elective percutaneous coronary intervention: results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty Platelet Reactivity for Outcome Validation Effort) study. *JACC Cardiovasc Interv* 2012;**5**:281–9	C
Mangiacapra F, Patti G, Gatto L, Nusca A, Vizzi V, Ricottini E, *et al.* Inadequate platelet inhibition with clopidogrel measured by a point-of-care assay and poorer peri-procedural outcome in diabetic patients undergoing percutaneous coronary intervention. *Eur Heart J* 2009;**30**:784	C
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Mangiacapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, *et al.* Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. *Am J Cardiol* 2010;**106**:619–23	C
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Mani H, Lindhoff-Last E. Response to Mortensen, *et al.* 'Do the Behring Coagulation Timer (BCT) and the Platelet Function Analyzer PFA-100 identify the same patients as being aspirin non-responder?' *Platelets* 2007;**18**:391–2	A
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Marcucci R, Giusti B, Gori AM, Paniccia R, Saracini C, Vestri A, *et al.* Cardiovascular death and nonfatal MI in ACS patients are predicted by residual platelet reactivity to ADP in the absence of CYP2C19*2 allele: beyond genetic screening. *Eur Heart J* 2009;**30**:197	C

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Article	Reason for exclusion
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Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, *et al.* Response to letter regarding article, 'cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up'. *Circulation* 2009;**120**:e99	A
Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, *et al.* Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. *Circulation* 2009;**119**:237–42	C
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Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation* 2007;**115**:2196–207	A
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Masik MG, Potapov BA, Kropel'nitskaia MV. [The status of the blood coagulation system during treatment of patients with diabetes mellitus.] *Vrach Delo* 1969;**10**:21–4	C, D
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Medeiros FB, de Andrade AC, Angelis GA, Conrado VC, Timerman L, Farsky P, *et al.* Bleeding evaluation during single tooth extraction in patients with coronary artery disease and acetylsalicylic acid therapy suspension: a prospective, double-blinded, and randomized study. *J Oral Maxillofac Surg* 2011;**69**:2949–55	D
Mehta AB, Mardikar HM, Shah S. Clopidogrel resistance: chemical curiosity or clinical enigma? *Indian Heart J* 2007;**59**:116–17	A
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Article	Reason for exclusion
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Mendolicchio GL, Zavalloni D, Corrada E, Rossi M, Marconi M, Bacci M, *et al.* Resistance to clopidogrel detected by real time evaluation of platelet thrombus formation. *J Thromb Haemost* 2009;**7**:896–7	C
Mendolicchio GL. Efficacy assessment of antiplatelet therapy in acute coronary syndrome by time-volume analysis of platelet thrombus formation. *Arterioscler Thromb Vasc Biol* 2010;**30**:e223	C
Mengistu AM, Mayer J, Boldt J, Rhm KD, Suttner SW. Usefulness of monitoring platelet function by multiple electrode aggregometry in primary coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2011;**25**:42–7	C, D
Merlini PA, Rossi M, Menozzi A, Buratti S, Brennan DM, Moliterno DJ, *et al.* Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation* 2004;**109**:2203–6	C
Mezzano D, Quiroga T, Pereira J. *The Level of Laboratory Testing Required for Diagnosis or Exclusion of a Platelet Function Disorder Using Platelet Aggregation and Secretion Assays*. New York, NY: Thieme; 2009	A
Michelson AD. Aspirin resistance. *Pathophysiol Haemost Thromb* 2006;**35**:5–9	A
Michelson AD. Evaluation of platelet function by flow cytometry. *Pathophysiol Haemost Thromb* 2006;**35**:67–82	A
Michelson AD. Platelet function testing in cardiovascular diseases. *Circulation* 2004;**110**:e489–93	A
Michelson AD. Platelet function testing in cardiovascular diseases. *Hematology* 2005;**10**(Suppl. 1):132–7	A
Migliorini A, Valenti R, Giuliani G, Buonamici P, Cerisano G, Carrabba N, *et al.* Prognostic impact of nonresponsivness platelet residual reactivity to clopidogrel therapy in patients with left main disease treated with coronary drug-eluting stent implantation. *Eur Heart J* 2009;**30**:847–8	B, C
Milovanovic M, Fransson E, Hallert C, Jaremo P. Atrial fibrillation and platelet reactivity. *Int J Cardiol* 2010;**145**:357–8	D
Mishra P, Kotwal J, Dutta V, Singh N, Kotwal A. Prevalence of aspirin and clopidogrel resistance in cardiac patients. *Indian J Hematol Blood Transfus* 2011;**27**:236	D
Moerenhout CM, Claeys MJ, Haine S, Miljoen H, Bosmans JM, Vertessen F, *et al.* Clinical relevance of clopidogrel unresponsiveness during elective coronary stenting: experience with the point-of-care platelet function assay-100 C/ADP. *Am Heart J* 2010;**159**:434–8	C
Mokhtar OA, Lemesle G, Armero S, Mancini J, Bonello C, Tahirou I, *et al.* Relationship between platelet reactivity inhibition and non-CABG related major bleeding in patients undergoing percutaneous coronary intervention. *Thromb Res* 2010;**126**:e147–9	C
Montalescot G, Sideris G, Meuleman C, Bal-Dit-Sollier C, Lellouche N, Steg PG, *et al.* A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 2006;**48**:931–8	C
Morel O, Bernhard N, Desprez D, Grunebaum L, Freyssinet JM, Toti F, *et al.* Residual prothrombotic status in low responder patients to clopidogrel identified by Vasodilator-Stimulated Phosphoprotein Phosphorylation (VASP) analysis? *Thromb Haemost* 2008;**99**:448–51	C, D
Morel O, El Ghannudi S, Jesel L, Radulescu B, Meyer N, Wiesel ML, *et al.* Cardiovascular mortality in chronic kidney disease patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12 inhibition by clopidogrel. *J Am Coll Cardiol* 2011;**57**:399–408	C
Morel O, Faure A, Ohlmann P, Jesel L, Desprez D, Grunebaum L, *et al.* Impaired platelet responsiveness to clopidogrel identified by flow cytometric vasodilator-stimulated phosphoprotein (VASP) phosphorylation in patients with subacute stent thrombosis. *Thromb Haemost* 2007;**98**:896–9	C
Moriyama Y, Toyohira H, Saigenji H, Shimokawa S, Taira A, Nakamura K. [Influence of acute aortic dissection, on platelet function second department of surgery, department of pharmacy: preliminary report.] *Nippon Geka Gakkai Zasshi* 1995;**96**:725	D
Morris A, Aliprandi-Costa B, Brieger D. Platelet function analysis: a comparison of methods. *Int J Cardiol* 2010;**145**:167–8	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Mortensen J, Poulsen TS, Refsgaard J, Kristensen SD. Do the Behring Coagulation Timer and the Platelet Function Analyzer-100 identify the same patients as being aspirin non-responders? *Platelets* 2007;**18**:389–90	A
Motoda C, Ueda H, Hayashi Y, Toyofuku M, Okimoto T, Otsuka M, *et al.* Impact of platelet reactivity to adenosine diphosphate before implantation of drug-eluting stents on subsequent adverse cardiac events in patients with stable angina. *Circ J* 2012;**76**:641–9	C
Motoyoshi K. Platelet function 2 weeks following stent implantation and its relation with factors for stent thrombosis. With special reference to the difference between silorimus-eluting and bare metal stents. *Teikyo Med J* 2007;**30**:111–20	D
Mueller C, Neumann FJ, Hochholzer W, Trenk D, Zeller T, Perruchoud AP, *et al.* The impact of platelet count on mortality in unstable angina/non-ST-segment elevation myocardial infarction. *Am Heart J* 2006;**151**:1214–17	C
Muir AR, McMullin MF, Patterson C, McKeown PP. Associations between methods of measurement of aspirin resistance and their temporal variations in patients with ischaemic heart disease. *Heart* 2008;**94**:A137	D
Muller-Schunk S, Linn J, Peters N, Spannagl M, Deisenberg M, Bruckmann H, *et al.* Monitoring of clopidogrel-related platelet inhibition: correlation of nonresponse with clinical outcome in supra-aortic stenting. *Am J Neuroradiol* 2008;**29**:786–91	C
Murray S. Does sex affect how patients respond to ASA? *CMAJ* 2006;**174**:773	A
Musumeci G, Valgimigli M, Sirbu V, Aprile A, Matiashvili A, Trivisonno A, *et al.* Correlation between stent strut coverage and platelet reactivity to predict outcome after coronary stenting. *Eur Heart J* 2009;**30**:674	D
Myers RI. The variability of platelet response to aspirin and clopidogrel: revisiting the Caprie, Cure, Credo, and Match trials. *Proc (Bayl Univ Med Cent)* 2005;**18**:331–6	A
Mylotte D, Foley D, Kenny D. Platelet function testing: methods of assessment and clinical utility. *Cardiovasc Hematol Agents Med Chem* 2011;**9**:14–24	A
Nagata Y, Kurokawa K, Inomata J, Aburatani I, Maruyama M, Usuda K. Usefulness of the platelet aggregately index in predicting atherothrombotic event in patient undergoing coronary intervention. *Am J Cardiol* 2011;**107**(Suppl. 1):29A	C
Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, *et al.* Platelet dysfunction is associated with worse outcome after intracerebral hemorrhage. *Stroke* 2009;**40**:e234	B
Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, *et al.* Platelet activity and outcome after intracerebral hemorrhage. *Ann Neurol* 2009;**65**:352–6	D
Naidech AM, Jovanovic B, Liebling S, Garg RK, Bassin SL, Bendok BR, *et al.* Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke* 2009;**40**:2398–401	B
Nava C, Recaldin E, Franchi F. [Hemocoagulation in myocardial infarct (thromboelastographic findings).] *Acta Gerontol (Milano)* 1967;**17**:146–68	B
Navarro-Nunez L, Pastor F, Lozano M, Marin F, Hurtado J, Roldan V, *et al.* Comparison of four tests to assess platelet reactivity in patients under dual antiplatelet therapy. *J Thromb Haemost* 2009;**7**:570	D
Nazarian SM, Thompson JB, Gluckman TJ, Laws K, Jani JT, Kickler TS, *et al.* Clinical and laboratory factors associated with shear-dependent platelet hyper-reactivity in patients on chronic aspirin therapy. *Thromb Res* 2010;**126**:379–83	D
Neubauer H, Kaiser AF, Endres HG, Kruger JC, Engelhardt A, Lask S, *et al.* Tailored antiplatelet therapy can overcome clopidogrel and aspirin resistance – the BOchum CLopidogrel and Aspirin Plan (BOCLA-Plan) to improve antiplatelet therapy. *BMC Med* 2011;**9**:3	D
Nezami N, Nargabad ON, Ghorashi S. Letter by Nezami, *et al.* regarding article, 'Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) trial'. *Circulation* 2012;**125**:e569	A

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Nishikawa M, Isshiki T, Ogawa H, Kimura T, Yokoi H, Nanto S, *et al.* Consistent and potent platelet inhibition of prasugrel irrespective of CYP2C19 polymorphism in Japanese patients with coronary artery disease. *J Thromb Haemost* 2011;**9**:336	C, D
Nitta M, Yano H, Endo T, Tsukahara K, Hibi K, Kimura K, *et al.* Contributing factors to high on-treatment residual platelet reactivity in patients with acute coronary syndromes. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E520	C
Noren I, Garde A. Value of blood coagulation tests in ischemic cerebral disease. *Eur Neurol* 1986;**25**:330–8	D
Nowakowski P. In reply to the comment on antiplatelet treatment monitoring. *Anest Intens Ter* 2007;**39**:164–5	A
Ntalianis A, Cuisset T, Hamilos M, Muller O, Mangiacapra F, Trana C, *et al.* PCI-related myocardial infarction in patients with renal insufficiency reloaded with clopidogrel: an open-label multicenter registry. *Eur Heart J* 2011;**32**:1039	C
Ntalianis A, Trana C, Muller O, Mangiacapra F, Peace A, Hamilos M, *et al.* Safety and efficacy of reloading doses of clopidogrel and aspirin before elective PCI to optimize periprocedural outcome in elderly. *Eur Heart J* 2010;**31**:221	D
Obergfell A, Strotmann J, Bonz A, Bauersachs J, Ertl G, Walter U, *et al.* Impaired platelet responses to clopidogrel and ticlopidine in a patient with recurrent coronary stent stenosis. *Thromb Haemost* 2004;**92**:1446–7	A
O'Brien JR. Platelet function tests and thrombosis. *Adv Exp Med Biol* 1972;**34**:43–54	A
O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, *et al.* Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;**374**:989–97	C
Oestreich JH, Steinhubl SR, Ferraris SP, Akers WS. High residual platelet reactivity on standard clopidogrel maintenance dose predicts increased responsiveness to the double-standard dose in an assay-dependent manner. *Thromb Haemost* 2011;**105**:927–30	C, D
Oh I-Y, Park KW, Kang S-H, Park JJ, Na S-H, Kang H-J, *et al.* Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents. *Heart* 2012;**98**:139–44	C
Oh I-Y, Yoon C-H, Park S-J, Park K-W, Lee H-Y, Cho H-J, *et al.* Cytochrome P450 2C19 loss-of-function polymorphism and cardiovascular events in patients treated with drug-eluting stent. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A113	C
Ohlmann P, El Ghannudi S, Wiesel M-L, Radulescu B, Bareiss P, Chauvin M, *et al.* Platelet reactivity assessed by flow cytometric vasp phosphorylation is an independent predictor of death and cardiovascular death in unselected patients undergoing PCI. *Am J Cardiol* 2009;**104**(Suppl. 1):171D	C
Okada K, Tsukahara K, Endo T, Hibi K, Uchino K, Umemura S, *et al.* Carriage of reduced-function CYP2C19 allele is an independent predictor of periprocedual myocardial infarction in patients with non ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E528	C
Oliveira DC, Silva RF, Silva DJ, Lima VC. Aspirin resistance: fact or fiction. *Arq Bras Cardiol* 2010;**95**:e91–4	A
Oliver WC, Kroening BJ, Waldo S, Diegel R, Brommer C, Schroeder D, *et al.* Coagulation tests predict bleeding in the intensive care unit after cardiac surgery. *Transfusion* 2010;**50**:180A–1A	B, C, D
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Oshima S, Noda K, Fukushima H, Nakamura S, Taniguchi I, Kugimiya F, *et al.* Platelet reactivity after thienopyridine treatment: assessment with screen filtration pressure method and drug-eluting stent thrombosis. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A171	C
Osmancik PP, Bednar F, Pavkova L, Tousek P, Stros P, Jirasek K. Higher platelet activity is present in patients with restenosis after percutaneous coronary intervention compared with patients with an occlusion of coronary artery bypass graft. *Blood Coagul Fibrinolysis* 2008;**19**:807–12	C, D
Ozben B, Tanrikulu AM, Ozben T, Caymaz O. Aspirin resistance in hypertensive patients. *J Clin Hypertens* 2010;**12**:714–20	D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Paikin J, Eikelboom JW, Brons S, Rokoss MJ, Valettas N, Velianou JL, *et al.* Distribution of response to clopidogrel therapy using vasodilator stimulated phosphoprotein assay in patients undergoing primary percutaneous coronary intervention for ST segment elevation myocardial infarction. *Can J Cardiol* 2011;**27**(Suppl. 1):S182–3	B, C
Paniccia R, Antonucci E, Maggini N, Romano E, Lucarini L, Rossi L, *et al.* Platelet reactivity in stable atherosclerotic disease patients on chronic antiplatelet treatment. *J Thromb Haemost* 2009;**7**:599–600	D
Papathanasiou A, Goudevenos J, Tselepis AD. Resistance to aspirin and clopidogrel: possible mechanisms, laboratory investigation, and clinical significance. *Hellenic J Cardiol* 2007;**48**:352–63	A
Papp E, Havasi V, Bene J, Komlosi K, Czopf L, Magyar E, *et al.* Glycoprotein IIIA gene (PlA) polymorphism and aspirin resistance: is there any correlation? *Ann Pharmacother* 2005;**39**:1013–18	D
Park D-W, Kim Y-G, Park G-M, Hwang K-W, Kwon C-H, Jang J-Y, *et al.* Differential prognostic implication of a point-of-care platelet function test in acute coronary syndrome versus stable angina after percutaneous coronary intervention. *Am J Cardiol* 2012;**109**(Suppl. 1):77–8	C
Park D-W, Kim Y-G, Park G-M, Hwang KW, Kwon CH, Jang JY, *et al.* Differential prognostic implication of a point-of-care platelet function test in patients with acute coronary syndrome versus stable angina and who undergoing percutaneous coronary intervention. *Circulation* 2011;**124**(Suppl. 1):A15095	B, C
Park D-W, Lee S-W, Yun S-C, Song H-G, Ahn J-M, Lee J-Y, *et al.* A point-of-care platelet function assay and C-reactive protein for prediction of major cardiovascular events after drug-eluting stent implantation. *J Am Coll Cardiol* 2011;**58**:2630–9	C
Park JH, Kim JS, Ahn C-M, Hong SJ, Choi JW, Ahn KJ, *et al.* A prospective multi-center study exploring method of clopidogrel pre-treatment undergoing conventional coronary angiogram in angina patients. *Am J Cardiol* 2012;**109**(Suppl. 1):136S	C, D
Park KW, Jeon KH, Kang SH, Oh IY, Cho HJ, Lee HY, *et al.* Clinical outcomes of high on-treatment platelet reactivity in Koreans receiving elective percutaneous coronary intervention (from results of the CROSS VERIFY study). *Am J Cardiol* 2011;**108**:1556–63	C
Parodi G, Bellandi B, Venditti F, Carrabba N, Valenti R, Migliorini A, *et al.* Residual platelet reactivity, bleedings, and adherence to treatment in patients having coronary stent implantation treated with prasugrel. *Am J Cardiol* 2012;**109**:214–18	C
Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, *et al.* High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. *JAMA* 2011;**306**:1215–23	C
Parodi G, Said K, Elfaramawy A, Hassan M, Marcucci R, Bellandi B, *et al.* Effectiveness of bivalirudin therapy in patients with high residual platelet activity after clopidogrel loading dose in patients undergoing elective percutanous coronary intervention: Six-month results from the Antithrombotic Regimens and Outcome (ARNO) trial. *J Am Coll Cardiol* 2010;**56**(Suppl. 1):B28	C
Pastor-Perez FJ, Rivera J, Hurtado JA, Navarro L, Ruiz-Nodar JM, Roldan V, *et al.* Residual platelet activation: too many methods for an accurate definition in clinical practice. *Eur Heart J* 2009;**30**:195	D
Patrono C. Aspirin resistance: definition, mechanisms and clinical read-outs. *J Thromb Haemost* 2003;**1**:1710–13	A
Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. *J Am Coll Cardiol* 2008;**52**:1128–33	C
Patti G, Nusca A. Influence of platelet reactivity on outcome of patients with acute myocardial infarction undergoing primary angioplasty. *Circ J* 2011;**75**:2050–1	A
Patti G, Pasceri V, Vizzi V, Ricottini E, Di Sciascio G. Usefulness of platelet response to clopidogrel by point-of-care testing to predict bleeding outcomes in patients undergoing percutaneous coronary intervention (from the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study). *Am J Cardiol* 2011;**107**:995–1000	C

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Payne DA, Jones CI, Hayes PD, Bell PRF, Goodal AH, Naylor AR. Effect of low-dose (75 mg) clopidogrel on platelet reactivity, ADP variability, and clopidogrel resistance when given before carotid surgery. *The Vascular Society Yearbook 2005*. London: The Vascular Society of Great Britain and Ireland; 2005. p. 48	D
Peace A, McCall M, Tedesco T, Kenny D, Conroy RM, Foley D, *et al.* The role of weight and enteric coating on aspirin response in cardiovascular patients. *J Thromb Haemost* 2010;**8**:2323–5	D
Peace AJ, Egan K, Kavanagh GF, Tedesco AF, Foley DP, Dicker P, *et al.* Reducing intra-individual variation in platelet aggregation: implications for platelet function testing. *J Thromb Haemost* 2009;**7**:1941–3	B, D
Perez de Prado A, Cuellas C, Diego A, de Miguel A, Fernandez-Vazquez F. Platelet reactivity and stent thrombosis: still some issues to solve. *J Am Coll Cardiol* 2009;**54**:666–7	A
Perez de Prado A, Cuellas C, Diego A, de Miguel A, Samaniego B, Alonso-Orcajo N, *et al.* Influence of platelet reactivity and response to clopidogrel on myocardial damage following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndrome. *Thromb Res* 2009;**124**:678–82	C
Petr R, Motovska Z, Marinov L, Bilkova D, Widimsky P. Resistance to clopidogrel assessed by VASP phosphorylation is a negative prognostic factor in patients undergoing elective PCI for stable coronary artery disease: Analysis from laboratory substudy of Prague 8 trial. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A98	C
Pham JP, Ueno M, Tello-Montoliu A, Ferreiro JL, Tomasello SD, Dharmashankar K, *et al.* Impact of gastric acid-suppressing therapies on platelet reactivity in patients with coronary artery disease treated with clopidogrel: results of a pharmacodynamic study. *J Am Coll Cardiol* 2011;**58**:1396–8	A
Piedade PR, Gagliardi RJ, Damiani IT, Nassar Junior AP, Fuzaro MM, Sanvito WL. [Platelet aggregation test: application in the control of antiplatelet aggregation in the secondary prevention of stroke.] *Arq Neuropsiquiatr* 2003;**61**:764–7	C
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Poston R, Gu J, Brown J, Gammie J, White C, Manchio J, *et al.* Hypercoagulability affecting early vein graft patency does not exist after off-pump coronary artery bypass. *J Cardiothorac Vasc Anesth* 2005;**19**:11–18	D
Poston R, Gu J, Manchio J, Lee A, Brown J, Gammie J, *et al.* Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting. *Eur J Cardiothorac Surg* 2005;**27**:584–91	D
Poston RS, Gu J, Brown JM, Gammie JS, White C, Nie L, *et al.* Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2006;**131**:122–30	D
Poston RS, Gu J, White C, Jeudy J, Nie L, Brown J, *et al.* Perioperative management of aspirin resistance after off-pump coronary artery bypass grafting: possible role for aprotinin. *Transfusion* 2008;**48**(Suppl.):39S–46S	D
Postula M, Tarchalska-Krynska B, Filipiak KJ, Kosior D, Serafin A, Huczek Z, *et al.* Factors responsible for 'aspirin resistance' – can we identify them? *Kardiol Pol* 2010;**68**:403–11	D
Poulsen TS, Kastrup A, Mickley H. Is aspirin resistance or female gender associated with a high incidence of myonecrosis after nonurgent percutaneous coronary intervention? *J Am Coll Cardiol* 2005;**45**:635–6	A
Poulsen TS, Kristensen SR, Atar D, Mickley H. A critical appraisal of the phenomenon of aspirin resistance: a review. *Cardiology* 2005;**104**:83–91	A
Pouplard C, Blicq E, Regina S, De Labriolle A, Charbonnier B, Gruel Y. Relation between cytochrome P450 2C19 681 G>A polymorphism, platelet responsiveness to ADP and clinical outcome after elective percutaneous coronary intervention in patients treated with clopidogrel. *J Thromb Haemost* 2009;**7**:1054	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Powers ER, Fowler A, Thieling C, Diaz-Gonzales V, Devlin M, Fernandes V, *et al.* Point-of-care testing of Platelet Function at the time of percutaneous coronary intervention identifies patients at risk for early post-procedure ischemia. *J Am Coll Cardiol* 2009;**53**:A69	D
Preisman S, Kogan A, Itzkovsky K, Leikin G, Raanani E. Modified thromboelastography evaluation of platelet dysfunction in patients undergoing coronary artery surgery. *Eur J Cardiothorac Surg* 2010;**37**:1367–74	D
Preisman S, Kogan A, Itzkovsky K, Leikin G, Raanani E. The risk of postoperative bleeding in patients receiving clopidogrel can be predicted using modified bedside thromboelastography. *Interact Cardiovasc Thorac Surg* 2009;**9**:S107	D
PRICE Investigators. Comparative 30-day economic and clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor use during elective percutaneous coronary intervention: Prairie ReoPro versus Integrilin Cost Evaluation (PRICE) trial. *Am Heart J* 2001;**141**:402–9	C
Price M, Lillie E, Angiolillo D, Teirstein P, Berger P, Tanguay JF, *et al.* Platelet reactivity on clopidogrel therapy and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent pharmacodynamic analysis of the GRAVITAS trial. *Eur Heart J* 2011;**32**:507–8	B, C
Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, *et al.* Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation* 2011;**124**:1132–7	B, C
Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, *et al.* Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;**305**:1097–105. [Erratum published in *JAMA* 2011;**305**:2174. Note: Stillablower, Michael E (corrected to Stillabower, Michael E)]	C
Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, *et al.* Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J* 2008;**29**:992–1000	C
Price MJ, Nayak KR, Barker CM, Kandzari DE, Teirstein PS. Predictors of heightened platelet reactivity despite dual-antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2009;**103**:1339–43	C
Price MJ. 'A threshold of platelet reactivity for ischaemic events?' and 'The optimal threshold of high post-treatment platelet reactivity could be defined by a point-of care VerifyNow P2Y12 assay': reply. *Eur Heart J* 2008;**29**:2187	A
Price MJ. Should routine platelet testing be done on all patients undergoing percutaneous coronary intervention? The evidence base for platelet function testing in patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2010;**3**:277–83	A
Price MJ. The evidence base for platelet function testing in patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2010;**3**:277–83. [Erratum published in *Circ Cardiovasc Interv* 2010;**3**:e18]	A
Prieto R, Martlnez-Selles M, Fernandez-Aviles F. Essential thrombocytemia and acute coronary syndrome: clinical profile and association with other thromboembolic events. *Acute Card Care* 2008;**10**:116–20	D
Qayyum R, Kral BG, Yanek LR, Vaidya D, Nyquist PA, Mathias R, *et al.* Greater post-aspirin residual platelet aggregation is associated with increased risk of incident acute coronary syndromes in healthy individuals. *Circulation* 2011;**124**(Suppl. 1):A16658	B
Qureshi H, Ahmed A, Dhillon JK. Evaluation of clinical and cost effectiveness of thromboelastography (TEG) in cardiac surgery. *Transfus Altern Transfus Med* 2010;**11**:38	D
Rade JJ, Gluckman TJ, McLean RC, Thompson JB, Thiemann DR, Laws K, *et al.* Aspirin-insensitive platelet hyper-reactivity and thromboxane generation are independent risk factors for early vein graft occlusion after coronary artery bypass surgery. *J Am Coll Cardiol* 2009;**53**:A334	D
Raman S, Jilma B. Time lag in platelet function inhibition by clopidogrel in stroke patients as measured by PFA-100. *J Thromb Haemost* 2004;**2**:2278–9	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Randall M, Storey RF, Venables GS, Gaines PA, Cleveland TJ. Variability in patient response to clopidogrel and effects on outcome from carotid stenting. *J Neurol Neurosurg Psychiatry* 2010;**81**:e69–70	C, D
Range G, Thuaire C, Richard P, Chassaing S, Belle L, Cazaux P, *et al.* Clinical impact of response to both aspirin and clopidogrel in 1001 patients undergoing coronary stenting: the one-year results of the multicenter Verifrenchy study. *Eur Heart J* 2010;**31**:154	D
Ranjadayalan K, Umachandran V, Timmis AD, Gutteridge CN. Platelet size and outcome after myocardial infarction. *Lancet* 1992;**339**:625	B
Ranucci M, Baryshnikova E, Soro G, Ballotta A, De Benedetti D, Conti D, *et al.* Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg* 2011;**91**:123–9	C
Ray MJ, Walters DL, Bett N, Cameron J, Wood P, Aroney C. Point-of-care testing shows clinically relevant variation in the degree of inhibition of platelets by standard-dose abciximab therapy during percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2004;**62**:150–4	B, C
Reed GW, Cannon CP. Personalized therapy following drug-eluting stenting using platelet function testing and C-reactive protein. *J Am Coll Cardiol* 2011;**58**:2640–1	A
Ren Y, Chen Y, Zhao M, Chen J, Chen L. Comparative study of aspirin and clopidogrel in high risk ACS. *Heart* 2010;**96**:A142–3	D
Ren YH, Yang TS, Wang Y, Gai LY, Liu HB, Chen L, *et al.* Evaluation of triple anti-platelet therapy by modified thrombelastography in patients with acute coronary syndrome. *Chin Med J* 2008;**121**:850–2	D
Renaud S. Risk factors for coronary heart disease and platelet functions. *Adv Exp Med Biol* 1984;**164**:129–44	A, B
Renda G, Sciartilli A, De Caterina R. Aspirin resistance. *Haematologica* 2003;**88**(Suppl. 4):43–9	A
Reny J-L, Berdague P, Combescure C, Nolli S, Barazer I, Fabbro-Peray P, *et al.* High residual platelet reactivity assessed with specific and global tests in the ADRIE study: comparative predictive values for the recurrence of ischemic events. *J Thromb Haemost* 2011;**9**:720	D
Reny J-L, Fontana P, Fabbro-Peray P, Laporte S, van Werkum JW, ten Berg JM, *et al.* Practical use and limitations of ADP aggregation testing to predict cardiovascular events: design and preliminary results of a meta-analysis on individual patients data. *J Thromb Haemost* 2011;**9**:337–8	C
Reny JL, Quere I, de Moerloose P, Fontana P. Aspirin response variability assessed with the PFA-100 device. *Thromb Haemost* 2008;**99**:968–9	A
Rha JH, Kim SR, Kim SH, Kim IG, Song CS, Choi YJ, *et al.* Relationships between laboratory antiplatelet resistance and clinical antiplatelet failure. *Cerebrovasc Dis* 2009;**27**:49	D
Ricottini E, Patti G, Vizzi V, Nusca A, Grieco D, Pasceri V, *et al.* A heightened platelet response to clopidogrel by point-of-care testing predicts bleeding outcomes in patients undergoing percutaneous coronary intervention. Results of armyda-bleeds (antiplatelet therapy for reduction of myocardial damage during angioplasty-bleeding study). *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1631	C
Rideg O, Komocsi A, Magyarlaki T, Tokes-Fuzesi M, Miseta A, Kovacs GL, *et al.* Impact of genetic variants on post-clopidogrel platelet reactivity in patients after elective percutaneous coronary intervention. *Pharmacogenomics* 2011;**12**:1269–80	C
Ripley AW, Narang J, Leitch S, Fifi J, Bennett H. Clopidogrel resistance in patients requiring endovascular neurological intervention. *J Neurosurg Anesthesiol* 2011;**23**:441	C
Rodzynek JJ, Leautaud P, Martin T, Schoenfeld PL, Wettendorff P, Delcourt A. Detection of a procoagulant activity in acute ischaemic heart disease. *Thromb Res* 1984;**33**:355–60	D
Rohatgi S, Aronow HD. Detection and management of aspirin resistance. *Crit Pathw Cardiol* 2004;**3**:177–83	A
Romashov VP. [Comparative evaluation of thromboelastographic data and some biochemical indices in myocardial infarct and stenocardia patients during anticoagulant therapy.] *Ter Arkh* 1964;**36**:11–17	B, D
Ronge R, Lindemann S, Gawaz M. Sex differences in platelet reactivity and response to aspirin therapy: Comment. *Dtsch Med Wochenschr* 2006;**131**:1990	A

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Rouvier J, Scazziota A, Altman R. Aspirin resistance. *Circulation* 2002;**106**:e200–1	A
Ryan WL, Hakenkamp K. Variable response to aspirin measured by platelet aggregation and bleeding time. *Lab Med* 1991;**22**:197–202	B, D
Ryu DS, Hong CK, Sim YS, Kim CH, Jung JY, Joo JY. Anti-platelet drug resistance in the prediction of thromboembolic complications after neurointervention. *J Korean Neurosurg Soc* 2010;**48**:319–24	D
Ryu J, Lee Y, Lee J, Choi J, Kim K, Chang S. Efficacy of high maintenance dose of clopidogrel to overcome high post treatment platelet P2Y12 reactivity after drug eluting coronary stent implantation. *Eur Heart J* 2010;**31**:976–7	D
Saad AA, Abd Elsalam AM, Kamal GM, Abou El-Ezz NF, El-Hagracy RS. Effect of cytochrome P450 3A5 polymorphism on platelet reactivity after treatment with clopidogrel in patients scheduled for percutaneous coronary intervention. *Egypt Heart J* 2011;**63**:23–31	C
Sacchi S, Curci G, Peduzzi M, Barbieri U, Piccinini L. Evaluation of platelet kinetics and some coagulation parameters in diabetic retinopathy. *Panminerva Med* 1981;**23**:21–4	D
Sadic BO, Tanrikulu MA, Koc M, Ozben T, Caymaz O. Aspirin resistance in patients with chronic renal failure. *Eur Heart J* 2010;**31**:966	D
Sahin DY, Koc M, Cayli M, Uysal OK, Karaarslan O, Kanadasi M, *et al.* [The frequency of aspirin resistance by a modified thrombelastography method and its relationship with clinical and laboratory parameters in patients with stable coronary artery disease.] *Turk Kardiyol Dernegi Ars* 2012;**40**:33–40	D
Sairaku A, Nakano Y, Eno S, Hondo T, Matsuda K, Kisaka T, *et al.* Platelet function measured using a whole blood aggregometer can predict bleeding events. *J Atheroscler Thromb* 2011;**18**:16–23	B, C
Salat A, Boehm D, Pulaki S, Murabito M, Berlakovich G, Kretschmer G, *et al.* Possibility of checking compliance and efficacy of antiaggregatory treatment following femoro-popliteal vein bypass surgery. *Thromb Res* 1998;**89**:91–5	D
Saleh N, Hansson LO, Kohut M, Nilsson T, Tornvall P. Platelet function and myocardial injury during percutaneous coronary intervention. *J Thromb Thrombolysis* 2002;**13**:69–73	D
Sambu N, Dent H, Warner T, Englyst N, Leadbeater P, Hobson A, *et al.* Stopping clopidogrel 1 year after drug-eluting stent (DES) implantation: is it safe? *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B41	D
Sambu N, Radhakrishnan A, Dent H, Calver A, Corbett S, Gray H, *et al.* The clopidogrel resistance in stent thrombosis (CREST) registry: the case for personalized antiplatelet therapy? *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B23	D
Sane DC, McKee SA, Malinin AI, Serebruany VL. Frequency of aspirin resistance in patients with congestive heart failure treated with antecedent aspirin. *Am J Cardiol* 2002;**90**:893–5	D
Sano K, Sugamata W, Deyama J, Uematsu M, Fujioka D, Nakamura T, *et al.* Usefulness of platelet retention assay for diagnosing acute coronary syndromes and predicting clinical outcome in patients with chest pain and/or shortness of breath. *Circulation* 2011;**124**(Suppl. 1):A9446	B, C
Sano T, Yamazaki H. [Progress in blood platelet function tests and anticipation of thrombosis.] *Nippon Rinsho* 1978;**36**:3836–41	A
Sansalvador V, Ezcurdia I. [Thromboelastographic study of the blood coagulation during the postoperative and postinfarct periods.] *Rev Clin Esp* 1964;**92**:185–8	B, C, D
Saraf S, Bensalha I, Gorog DA. Antiplatelet resistance – does it exist and how to measure it? *Clin Med Cardiol* 2009;**3**:77–91	A
Saraf S, Christopoulos C, Salha IB, Stott DJ, Gorog DA. Impaired endogenous thrombolysis in acute coronary syndrome patients predicts cardiovascular death and nonfatal myocardial infarction. *J Am Coll Cardiol* 2010;**55**:2107–15	C
Sarafoff N, Neumann L, Morath T, Bernlochner I, Mehilli J, Schomig A, *et al.* Impact of calcium channel blockers on the pharmacodynamic effect and the clinical efficacy of clopidogrel after drug eluting stenting. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E1913	B, C

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Sarafoff N, Neumann L, Morath T, Bernlochner I, Mehilli J, Schomig A, *et al.* Lack of impact of calcium-channel blockers on the pharmacodynamic effect and the clinical efficacy of clopidogrel after drug-eluting stenting. *Am Heart J* 2011;**161**:605–10	C
Sardella G, Calcagno S, De Carlo C, Pennacchi M, Placentino F, Stio R, *et al.* Pharmacodynamic effects of switching therapy in PCI patients with high on treatment platelet reactivity and genotype variation: high clopidogrel dose versus prasugrel (reset trial). *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E6	C
Sardi G, Zaheeruddin S, Pakala R, Carnicero AL, Torguson R, Badr S, *et al.* Does on-treatment platelet reactivity testing before coronary artery bypass surgery have a value in predicting in-hospital major bleeding? *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E261	C
Sarkiss MG, Yusuf SW, Warneke CL, Botz G, Lakkis N, Hirch-Ginsburg C, *et al.* Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. *Cancer* 2007;**109**:621–7	C, D
Sarode R, Frenkel E. And, more on: assessing aspirin responsiveness using the VerifyNow aspirin assay. *Thromb Res* 2008;**121**:587–8	A
Saunders J, Nambi V, Kimball KT, Virani SS, Morrisett JD, Lumsden AB, *et al.* Variability and persistence of aspirin response in lower extremity peripheral arterial disease patients. *J Vasc Surg* 2011;**53**:668–75	D
Saunders JT, Nambi V, Virani S, Yang E, Bergeron A, Athamneh H, *et al.* Twelve month persistence of poor response to aspirin in patients with peripheral arterial disease enrolled in the effect of lipid modification on peripheral arterial disease after endovascular intervention trial (ELIMIT). *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A155	D
Scalone G, Coviello I, Barone L, Battipaglia I, Aurigemma C, Careri G, *et al.* Evidence of increased platelet reactivity in the first six months after acute ST segment elevation myocardial infarction. *Thromb Res* 2011;**128**:174–8	C, D
Schaefer A, Flierl U, Seydelmann N, Bauersachs J. Impaired P2Y12 inhibition contributes to increased cardiovascular events following prehospital administration of clopidogrel in patients with ST elevation myocardial infarction. *Eur Heart J Suppl* 2010;**12**:F52–3	C
Schafer A, Bonz AW, Eigenthaler M, Bauersachs J. Late thrombosis of a drug-eluting stent during combined anti-platelet therapy in a clopidogrel nonresponsive diabetic patient: shall we routinely test platelet function? *Thromb Haemost* 2007;**97**:862–5	A
Schafer A, Flierl U, Kossler J, Seydelmann N, Kobsar A, Stork S, *et al.* Early determination of clopidogrel responsiveness by platelet reactivity index identifies patients at risk for cardiovascular events after myocardial infarction. *Thromb Haemost* 2011;**106**:141–8	C
Scheen AJ, Legrand D. Aspirin and clopidogrel resistance in patients with diabetes mellitus. *Eur Heart J* 2006;**27**:2900–1	A
Scheinowitz M, Slottow TLP, Pakala R, Baffour R, Bonello L, Torguson R, *et al.* Elevated circulating endothelial progenitor cells in stent thrombosis patients is not correlated with platelet reactivity index. *J Am Coll Cardiol* 2009;**53**:A13	B, C
Schneider DJ, Herrmann HC, Lakkis N, Aguirre F, Wan Y, Aggarwal A, *et al.* Enhanced early inhibition of platelet aggregation with an increased bolus of tirofiban. *Am J Cardiol* 2002;**90**:1421–3	C
Schneider DJ. On defining aspirin resistance. *J Am Coll Cardiol* 2005;**46**:1710–11	A
Schreiber TL, Macina G, Bunnell P, Tenney RD, McNulty A, Kikel M, *et al.* Unstable angina or non-Q wave infarction despite long-term aspirin: response to thrombolytic therapy with implications on mechanisms. *Am Heart J* 1990;**120**:248–55	C
Schror K, Huber K, Hohlfeld T. Functional testing methods for the antiplatelet effects of aspirin. *Biomarkers Med* 2011;**5**:31–42	A
Schror K. What is aspirin resistance? *Br J Cardiol* 2010;**17**(Suppl. 1):S5–7	A
Schulz S, Sibbing D, Braun S, Morath T, Mehilli J, Massberg S, *et al.* Platelet response to clopidogrel and restenosis in patients treated predominantly with drug-eluting stents. *Am Heart J* 2010;**160**:355–61	C
Schulz S, Sibbing D, Morath T, von Beckerath N, Mehilli J, Byrne RA, *et al.* Does platelet reactivity to clopidogrel effect restenosis after DES implantation? *Eur Heart J* 2009;**30**:199	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Schwartz MB, Hawiger J, Timmons S, Friesinger GC. Platelet aggregates in ischemic heart disease. *Thromb Haemost* 1980;**43**:185–8	B
Schwonberg J, Linnemann B, Toennes SW, Mani H, Lindhoff-Last E. Variability of residual platelet function despite clopidogrel treatment in patients with peripheral arterial occlusive disease – a prospective study. *J Thromb Haemost* 2009;**7**:897	B
Scirica BM, Cannon CP, Cooper R, Aster RH, Brassard J, McCabe CH, *et al.* Drug-induced thrombocytopenia and thrombosis: evidence from patients receiving an oral glycoprotein IIb/IIIa inhibitor in the Orbofiban in Patients with Unstable coronary Syndromes (OPUS-TIMI 16) trial. *J Thromb Thrombolysis* 2006;**22**:95–102	C
Seidel H, Rahman MM, Scharf RE. Monitoring of antiplatelet therapy. Current limitations, challenges, and perspectives. *Hamostaseologie* 2011;**31**:41–51	A
Selvaraj CL, Van De Graaff EJ, Campbell CL, Abels BS, Marshall JP, Steinhubl SR. Point-of-care determination of baseline platelet function as a predictor of clinical outcomes in patients who present to the emergency department with chest pain. *J Thromb Thrombolysis* 2004;**18**:109–15	C
Serebruany V, McKenzie M, Meister A, Fuzaylov S, Gurbel P, Atar D, *et al.* Whole blood impedance aggregometry for the assessment of platelet function in patients with congestive heart failure (EPCOT trial). *Eur J Heart Fail* 2002;**4**:461–7	C, D
Serebruany V. Lack of outcome benefit and clopidogrel 'resistance.' The TRITON trial challenge. *Thromb Haemost* 2010;**103**:415–18	A
Serebruany VL, Goto S. The challenge of monitoring platelet response after clopidogrel. *Eur Heart J* 2008;**29**:2833–4	A
Serebruany VL, McKenzie ME, Meister AF, Fuzaylov SY, Gurbel PA, Atar D, *et al.* Failure of platelet parameters and biomarkers to correlate platelet function to severity and etiology of heart failure in patients enrolled in the EPCOT trial. With special reference to the Hemodyne hemostatic analyzer. Whole blood impedance aggregometry for the assessment of platelet function in patients with congestive heart failure. *Pathophysiol Haemost Thromb* 2002;**32**:8–15	D
Sevcikova H, Vojacek J, Bis J, Sevcik R, Maly J, Pecka M, *et al.* Good short-term but not long-term reproducibility of the antiplatelet efficacy laboratory assessment. *Clin Appl Thromb Hemost* 2012;**18**:174–80	D
Shalaev SV. [Development of myocardial infarction in aspirin-treated unstable angina pectoris. Repeated studies of platelet aggregation and of the thromboxane-prostacyclin system.] *Kardiologiia* 1992;**32**:27–30	D
Shal'nov AI. [Ischemic heart disease and blood coagulation (data on the epidemiological examination of men 40–59 years of age by thrombelastography).] *Ter Arkh* 1981;**53**:41–6	C, D
Shantsila E, Lip GY. Beyond glucose levels in diabetic patients with coronary artery disease: platelet activity and non-responsiveness to antiplatelet therapy. *Thromb Haemost* 2008;**100**:7–8	A
Shantsila E, Watson T, Lip GY. Aspirin resistance: what, why and when? *Thromb Res* 2007;**119**:551–4	A
Sharma RK, Reddy HK, Singh VN, Sharma R, Voelker DJ, Bhatt G. Aspirin and clopidogrel hyporesponsiveness and nonresponsiveness in patients with coronary artery stenting. *Vasc Health Risk Manag* 2009;**5**:965–72	A
Sharma RK, Voelker DJ, Sharma R, Reddy HK, Dod H, Marsh JD. Evolving role of platelet function testing in coronary artery interventions. *Vasc Health Risk Manag* 2012;**8**:65–75	A
Sharma S, Moffat D, Christopoulous C, Klonizakis M, Wellstead D, Farrington K, *et al.* Global thrombotic status predicts cardiovascular events in end-stage renal failure. *Eur Heart J* 2010;**31**:971	B, C
Sharma V, Kaul S, Al-Hazzani A, Prabha TS, Rao PPKM, Dadheech S, *et al.* Association of C3435T multi drug resistance gene-1 polymorphism with aspirin resistance in ischemic stroke and its subtypes. *J Neurol Sci* 2012;**315**:72–6	C
Sharp DS, Ben-Shlomo Y, Beswick AD, Andrew ME, Elwood PC. Platelet aggregation in whole blood is a paradoxical predictor of ischaemic stroke: Caerphilly prospective study revisited. *Platelets* 2005;**16**:320–8	C
Shechter M, Merz CN, Paul-Labrador MJ, Kaul S. Blood glucose and platelet-dependent thrombosis in patients with coronary artery disease. *J Am Coll Cardiol* 2000;**35**:300–7	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Shen J, Zhang RY, Zhang Q. [Impact of statins on clopidogrel platelet inhibition in patients with acute coronary syndrome or stable angina.] *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih* 2008;**36**:807–11	D
Shi ZW. [Aspirin resistant concept gives no guide to clinical application.] *Chung-Hua Nei Ko Tsa Chih* 2008;**47**:269–71	A
Shimbo D, Child J, Davidson K, Geer E, Osende JI, Reddy S, *et al.* Exaggerated serotonin-mediated platelet reactivity as a possible link in depression and acute coronary syndromes. *Am J Cardiol* 2002;**89**:331–3	B, D
Shimomura H, Hokimoto S, Ogawa H. Clinical outcomes following coronary stenting in Japanese patients with and without proton pump inhibitor. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A52	C
Sholokhova GI, Iakovleva IM. [Thromboelastogram in ischemic heart disease.] *Kardiologiia* 1973;**13**:130–2	B, C, D
Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schomig A, *et al.* Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. *J Am Coll Cardiol* 2009;**53**:849–56	C
Sibbing D, Byrne RA, Bernlochner I, Kastrati A. High platelet reactivity and clinical outcome – fact and fiction. *Thromb Haemost* 2011;**106**:191–202	A
Sibbing D, Byrne RA, Kastrati A. Role of platelet function testing in clinical practice: current concepts and future perspectives. *Curr Drug Targets* 2011;**12**:1836–47	A
Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, *et al.* Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* 2010;**121**:512–18	C
Sibbing D, Mayer K, Bernlochner I, Morath T, Jaitner J, Haase U, *et al.* Platelet function testing guided use of prasugrel in patients with high on-clopidogrel treatment platelet reactivity reduces the risk of early stent thrombosis. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E265	C
Sibbing D, Morath T, Braun S, Stegherr J, Mehilli J, Vogt W, *et al.* Clopidogrel response status assessed with Multiplate point-of-care analysis and the incidence and timing of stent thrombosis over six months following coronary stenting. *Thromb Haemost* 2010;**103**:151–9	C
Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, *et al.* Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. *J Thromb Haemost* 2010;**8**:250–6	C
Sibbing D, Steinhubl SR, Schulz S, Schomig A, Kastrati A. Platelet aggregation and association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. *Eur Heart J* 2010;**31**:147	B, C
Sibbing D, Taubert D, Schomig A, Kastrati A, von Beckerath N. Pharmacokinetics of clopidogrel in patients with stent thrombosis. *J Thromb Haemost* 2008;**6**:1230–2	C, D
Sibbing D, von Beckerath O, Schomig A, Kastrati A, von Beckerath N. Diabetes mellitus and platelet function after administration of aspirin and a single 600 mg dose of clopidogrel. *J Thromb Haemost* 2006;**4**:2566–8	C
Siegemund A, Korner I, Scholz U. Monitoring of antiplatelet agents – necessary in patients with cardiovascular diseases? *J Thromb Haemost* 2009;**7**:877	D
Silagy CA, McNeil JJ, Donnan GA, Tonkin AM, Worsam B, Campion K. The PACE pilot study: 12-month results and implications for future primary prevention trials in the elderly. (Prevention with low-dose Aspirin of Cardiovascular disease in the Elderly). *J Am Geriatr Soc* 1994;**42**:643–7	B
Siller-Matula J, Delle KG, Lang IM, Neunteufl T, Kozinski M, Kubica J, *et al.* Phenotyping versus genotyping for prediction of adverse events in clopidogrel non-responders. *J Kardiol* 2011;**18**:189	B, C
Siller-Matula JM, Christ G, Lang IM, le-Karth G, Huber K, Jilma B. Multiple electrode aggregometry predicts stent thrombosis better than the vasodilator-stimulated phosphoprotein phosphorylation assay. *J Thromb Haemost* 2010;**8**:351–9	C
Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. *J Am Coll Cardiol* 2008;**52**:1557–63	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Siller-Matula JM, le-Karth G, Lang IM, Neunteufl T, Kozinski M, Kubica J, *et al.* Phenotyping vs. genotyping for prediction of clopidogrel efficacy and safety: the PEGASUS-PCI study. *J Thromb Haemost* 2012;**10**:529–42	C
Siller-Matula JM, le-Karth G, Neunteufl T, Lang I, Kozinski M, Kubica J, *et al.* Phenotyping versus genotyping for prediction of adverse events in clopidogrel non-responders. *Eur Heart J* 2011;**32**:172	B, C
Simoons ML, de Boer MJ, van den Brand MJ, van Miltenburg AJ, Hoorntje JC, Heyndrickx GR, *et al.* Randomized trial of a GPIIb/IIIa platelet receptor blocker in refractory unstable angina. European Cooperative Study Group. *Circulation* 1994;**89**:596–603	C, D
Simpfendorfer C, Kottke-Marchant K, Lowrie M, Anders RJ, Burns DM, Miller DP, *et al.* First chronic platelet glycoprotein IIb/IIIa integrin blockade. A randomized, placebo-controlled pilot study of xemilofiban in unstable angina with percutaneous coronary interventions. *Circulation* 1997;**96**:76–81	C
Simpson SH, Gamble JM, Mereu L, Chambers T. Effect of aspirin dose on mortality and cardiovascular events in people with diabetes: a meta-analysis. *J Gen Intern Med* 2011;**26**:1336–44	C
Singh A, Feit F, Bangalore S. Does triple therapy with cilostazol decrease platelet reactivity in patients undergoing percutaneous coronary intervention? A meta analysis of randomized clinical trials. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E527	C
Singh A, Gupta OP, Sangha HK. Platelet function tests in acute myocardial infarction. *Indian Heart J* 1980;**32**:25–9	B, D
Singh M, Shah T, Singh P, Adigopula S, Kodumuri V, Molnar J, *et al.* Platelet function tests predict a relationship between on-treatment platelet reactivity and clinical outcome in patients undergoing percutaneous coronary intervention. *Circulation* 2011;**124**(Suppl. 1):A12086	B, C
Singh S, Kothari SS, Bahl VK. Aspirin resistance: myth or reality? *Indian Heart J* 2003;**55**:217–22	A
Smit JJJ, van Werkum JW, Heestermans AACM, Postma S, Hermanides RS, Dill T, *et al.* Insufficient platelet aggregation inhibition by pre-hospital clopidogrel alone vs additional high dose Tirofiban in patients with acute STEMI undergoing primary PCI resulting in worse clinical outcome. *Eur Heart J* 2009;**30**:193–4	B
Smith JP, Haddad EV, Boutaud O, Oram DA, Blakemore DL, Chen QX, *et al.* Metabolic syndrome associates with resistance to aspirin in patients with coronary artery disease. *Circulation* 2009;**120**:S1033	D
Smith PS. Who can resist aspirin? *Nursing* 2005;**35**:20	A
Smitherman TC, Milam M, Woo J, Willerson JT, Frenkel EP. Elevated beta thromboglobulin in peripheral venous blood of patients with acute myocardial ischemia: direct evidence for enhanced platelet reactivity in vivo. *Am J Cardiol* 1981;**48**:395–402	B, C, D
Smout J, Cleanthis M, Stansby G. Comment on 'hyperresponsiveness of platelets in ischemic stroke' by Fateh-Moghadam *et al. Thromb Haemost* 2008;**99**:239	A
Smout J, Stansby G. Aspirin resistance. *Br J Surg* 2002;**89**:4–5	A
Snoep JD, Eikenboom JCJ, Zwaginga JJ, Roest M, Patrono C, Rocca B, *et al.* Platelet reactivity and recurrent cardiovascular events in patients with stable cardiovascular disease using aspirin: a head-to-head comparison of different tests. *J Thromb Haemost* 2011;**9**:16	D
Snoep JD, Hovens MMC, Eikenboom JCJ, Van Der Bom JG, Huisman MV. Is aspirin resistance due to noncompliance? – reply. *Arch Intern Med* 2008;**168**:550	A
Snoep JD, Hovens MMC, Eikenboom JCJ, Van Der Bom JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J* 2007;**154**:221–31	C
Snoep JD, Roest M, Barendrecht A, Rosendaal FR, Van Der Bom JG. High platelet reactivity and the risk of myocardial infarction in young women. *J Thromb Haemost* 2009;**7**:275	D
Sobol AB, Selmaj K, Mochecka A, Kumor A, Loba J. Aspirin responsiveness in ischemic stroke patients in relation to diabetes mellitus, lipid and hemostatic profile. *Adv Clin Exp Med* 2010;**19**:593–9	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Soffer D, Moussa I, Karatepe M, Harjai KJ, Boura J, Dixon SR, *et al.* Suboptimal inhibition of platelet aggregation following tirofiban bolus in patients undergoing percutaneous coronary intervention for unstable angina pectoris. *Am J Cardiol* 2003;**91**:872–5	C, D
Sofi F, Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF. Clopidogrel non-responsiveness and risk of cardiovascular morbidity. An updated meta-analysis. *Thromb Haemost* 2010;**103**:841–8	C
Mayo Clinic. Some people are resistant to aspirin's protective effects. *Mayo Clin Health Lett* 2004;**22**:4	A
Song T-J, Lee J-B, Suh S-H, Lee K-Y. The influence of anti-platelet resistance for the development of silent ischemia after carotid artery stenting. *Int J Stroke* 2010;**5**:162	D
SoRelle R. Resisting aspirin. *Circulation* 2002;**105**:e9094–5	A
Sorensen EN, Snyder TA, Lindsay MJ, Moainie SL, Feller ED, Griffith BP. Seven-fold stroke reduction in Ventricular-Assist Device (VAD) patients with titrated antiplatelet therapy. *J Heart Lung Transplant* 2009;**28**(Suppl. 1):S154	C
Steinhubl SR, Campbell CL. Variability in response to aspirin: do we understand the clinical relevance? *J Thromb Haemost* 2005;**3**:665–9	A
Steinhubl SR, Varanasi JS, Goldberg L. Determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 2003;**42**:1336–7. [Erratum published in *J Am Coll Cardiol* 2004;**43**:154. Note: Varinasi JS (corrected to Varanasi JS)]	A
Steinhubl SR, Varanasi JS, Goldberg L. Determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 2003;**42**:1336. [Erratum published in *J Am Coll Cardiol* 2004;**43**:154]	A
Steinhubl SR. The illusion of 'optimal' platelet inhibition. *JACC Cardiovasc Interv* 2012;**5**:278–80	A
Stiefelhagen P, Krasopoulos G. Aspirin resistance increases cardiovascular risk. *MMW-Fortschr Med* 2009;**151**:27	A
Strano A, Davi G. Platelet function tests and coronary heart disease. *Adv Exp Med Biol* 1984;**164**:31–47	A
Suchkova EN. [Blood coagulation capacity in patients with diabetes mellitus according to biochemical and thromboelastographic data.] *Ter Arkh* 1965;**37**:80–5	C, D
Sudkamp M, Mehlhorn U, Reza RM, Hekmat K, Easo J, Geissler HJ, *et al.* Cardiopulmonary bypass copolymer surface modification reduces neither blood loss nor transfusions in coronary artery surgery. *Thorac Cardiovasc Surg* 2002;**50**:5–10	C, D
Suh J-W, Kim C-H, Oh I-Y, Yoon C-H, Cho Y-S, Youn T-J, *et al.* The effect of tailored antiplatelet therapeutic strategy during percutaneous coronary intervention on periprocedural myonecrosis in diabetic patients: insights from the DM-verifynow study. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E1532	C
Suh JW, Lee SP, Park KW, Lee HY, Kang HJ, Koo BK, *et al.* Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the CILON-T (influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) trial. *J Am Coll Cardiol* 2011;**57**:280–9	C
Sung JK, Yoon YJ, Lee NS, Lee JW, Kim J-Y, Lee SH, *et al.* The effect of clopidogrel low-responsiveness assessed by VerifyNow P2Y12 assay on thrombotic events after implantation of drug-eluting stent. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A206	C
Suslina ZA, Tanashian MM, Domashenko MA. [Resistance to antiplatelet drugs in patients with cerebrovascular disorders.] *Vestn Ross Akad Med Nauk* 2011;**7**:3–8	A
Szczeklik A, Musial J, Undas A. Reasons for resistance to aspirin in cardiovascular disease. *Circulation* 2002;**106**:e181–2	A
Szczeklik A, Undas A. More on: aspirin resistance. *J Thromb Haemost* 2004;**2**:1489	A
Szczeklik A. Reasons for aspirin resistance. *Thromb Haemost* 2011;**105**:1124	A
Szymezak J, Moreau C, Loriot MA, Durand E, Van Viet H, Desnos M, *et al.* High on-clopidogrel platelet reactivity: genotyping can help to optimize antiplatelet treatment. *Thromb Res* 2011;**128**:92–5	C

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Takatsu Y, Yui Y, Hattori R, Sakaguchi K, Susawa T, Yui N, *et al.* Platelet aggregation and thromboxane B2 release in patients with acute myocardial infarction – their relation to coronary patency. *Jpn Circ J* 1988;**52**:314–20	B
Tanaka KA, Szlam F, Kelly AB, Vega JD, Levy JH. Clopidogrel (Plavix) and cardiac surgical patients: implications for platelet function monitoring and postoperative bleeding. *Platelets* 2004;**15**:325–32	D
Tanboga IH, Tokgoz HC, Can MM, Bezgin T, Turkyilmaz E, Akgun T, *et al.* The polymorphisms of CYP2C19, CYP3A5 and CYP2C9 enzymes in relation to platelet response to clopidogrel as assessed by multiplate analyser and long-term clinical outcome. *Eur Heart J* 2010;**31**:1017–18	B
Tanigawa T, Nishikawa M, Kitai T, Ueda Y, Okinaka T, Makino K, *et al.* Increased platelet aggregability in response to shear stress in acute myocardial infarction and its inhibition by combined therapy with aspirin and cilostazol after coronary intervention. *Am J Cardiol* 2000;**85**:1054–9	D
Tanrikulu AM, Ozben B, Koc M, Papila-Topal N, Ozben T, Caymaz O. Aspirin resistance in patients with chronic renal failure. *J Nephrol* 2011;**24**:636–46	D
Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. *J Am Coll Cardiol* 2005;**46**:1705–9	D
Tantry US, Jeong Y-H, Navarese EP, Gurbel PA. Platelet function measurement in elective percutaneous coronary intervention patients: exploring the concept of a P2Y12 inhibitor therapeutic window. *JACC Cardiovasc Interv* 2012;**5**:290–2	A
Tantry US, Mahla E, Gurbel PA. Aspirin resistance. *Prog Cardiovasc Dis* 2009;**52**:141–52	A
Tantry US, Bliden KP, Suarez TA, Kreutz RP, Dichiara J, Gurbel PA. Hypercoagulability, platelet function, inflammation and coronary artery disease acuity: results of the Thrombotic RIsk Progression (TRIP) study. *Platelets* 2010;**21**:360–7	D
Tantry US, Gurbel PA. Assessment of oral antithrombotic therapy by platelet function testing. *Nat Rev Cardiol* 2011;**8**:572–9	A
Taomoto K, Ohnishi H, Kuga Y, Nakashima K, Kodama Y, Kubota H, *et al.* Clinical outcome and platelet function of acute stroke by global thrombosis test (GTT) after t-PA therapy. *J Thromb Haemost* 2011;**9**:84	B, C, D
Tarjan J, Salamon A, Jager R, Poor F, Barczi V, Dinnyes J, *et al.* [The rate of acetylsalicylic acid non-respondents among patients hospitalized for acute coronary disease, previously undergoing secondary salicylic acid prophylaxis.] *Orvosi Hetil* 1999;**140**:2339–43	D
Tarzia V, Paolini C, Bottio T, Rizzoli G, Spiezia L, Dal LC, *et al.* Perioperative hemostasis and bleeding risk in double-antiplatelet high risk patients undergoing coronary revascularization procedure. A prospective controlled study. *Eur Heart J* 2010;**31**:62	C, D
Tefferi A. Overcoming 'aspirin resistance' in MPN. *Blood* 2012;**119**:3377–8	A
Tello-Montoliu A, Jover E, Marin F, Bernal A, Lozano ML, Sanchez-Vega B, *et al.* Influence of CYP2C19 polymorphisms in on-treatment platelet reactivity and prognosis in an unselected population of non ST elevation acute coronary syndrome. *Eur Heart J* 2011;**32**:264	C
Tello-Montoliu A, Jover E, Marin F, Bernal A, Lozano ML, Sanchez-Vega B, *et al.* Influence of CYP2C19 polymorphisms in platelet reactivity and prognosis in an unselected population of non ST elevation acute coronary syndrome. *Rev Esp Cardiol (Engl Ed)* 2012;**65**:219–26	C
ten Berg JM. Error in a study of the comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary artery stent implantation. *JAMA* 2011;**305**:2172–3. [Erratum for *JAMA* 2010;**303**:754–62]	A
Thani KB, Ilapakurti M, Ang L, Prasad A, Palakodeti V, Mahmud E. Increased incidence of peri-procedural myocardial infarction in patients pre-treated with clopidogrel and undergoing percutaneous coronary intervention: role of fibrinogen and platelet reactivity. *Catheter Cardiovasc Interv* 2010;**75**:S59	B
Theakos N, Dedeilias P, Argiriou M, Roussakis A, Patronis M, Bolos K. Postoperative aspirin and clopidogrel resistance in patients submitted to on-pump coronary artery bypass surgery. *Interact Cardiovasc Thorac Surg* 2009;**9**:S106	D

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Thomas M, Wijeyeratne Y, May J, Fox S, Heptinstall S. P-selectin is associated with subsequent atherothrombotic events in patients with recent acute coronary syndromes treated with clopidogrel. *J Thromb Haemost* 2011;**9**:743	C
Tidiane AM, Ghenim R, Bongard V, Boudou N, Dumonteil N, Hammami N, *et al.* Assessment of dual antiplatelet responsiveness with the point-of-care device verifynow after percutaneous coronary intervention in elderly patients (> 75 years). *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A171	D
Tidjane AM, Ghenim R, Bongard V, Boudou N, Dumonteil N, Hammami N, *et al.* Natural history of dual anti-platelet responsiveness after angioplasty in elderly patients. *Arch Cardiovasc Dis Suppl* 2010;**2**:15	D
Tirosh-Wagner T, Strauss T, Rubinshtein M, Tamarin I, Mishaly D, Paret G, *et al.* Point of care testing in children undergoing cardiopulmonary bypass. *Pediatr Blood Cancer* 2011;**56**:794–8	B
Tobin WO, Kinsella JA, Collins DR, Coughlan T, O'Neill D, Egan B, *et al.* Enhanced ex vivo inhibition of platelet function following addition of dipyridamole to aspirin after transient ischaemic attack or ischaemic stroke: first results from the TRinity AntiPlatelet responsiveness (TrAP) study. *Br J Haematol* 2011;**152**:640–7	D
Tobin WO, Kinsella JA, Collins DR, Coughlan T, O'Neill D, Feeley TM, *et al.* Enhanced ex vivo inhibition of platelet function after addition of dipyridamole to aspirin in ischaemic cerebrovascular disease – interim results from the trinity antiplatelet responsiveness study. *J Neurol Neurosurg Psychiatry* 2009;**80**:e1	D
Tobin WO, Kinsella JA, Murphy RP, Collins DR, Coughlan T, O'Neill D, *et al.* Circulating reticulated platelets influence the ex vivo response to aspirin, but not dipyridamole or clopidogrel, in the early phase after TIA or ischaemic stroke – initial results from the trinity antiplatelet responsiveness (TRAP) study. *Cerebrovasc Dis* 2011;**31**:142	D
Tobin WO, Kinsella JA, Murphy RP, Collins DR, Coughlan T, O'Neill D, *et al.* Novel longitudinal definitions of aspirin and clopidogrel 'non-responsiveness' on the PFA-100: results from the trinity antiplatelet responsiveness (TRAP) study. *Cerebrovasc Dis* 2011;**31**:139	D
Topcuoglu MA, Arsava EM, Ay H. Antiplatelet resistance in stroke. *Expert Rev Neurother* 2011;**11**:251–63	A
Tousek P, Osmancik P, Paulu P, Kocka V, Widimsky P. Clopidogrel up-titration versus standard dose in patients with high residual platelet reactivity after percutaneous coronary intervention: a single-center pilot randomised study. *Int J Cardiol* 2011;**150**:231–2	C
Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, *et al.* Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008;**51**:1925–34	C
Trenk D, Hochholzer W, Fromm MF, Zolk O, Valina CM, Stratz C, *et al.* No association of paraoxonase-1 Q192R genotype with antiplatelet effects of clopidogrel in patients undergoing elective coronary stent placement. *Br J Clin Pharmacol* 2011;**72**:8	B
Trenk D, Hochholzer W, Fromm MF, Zolk O, Valina CM, Stratz C, *et al.* Paraoxonase-1 Q192R polymorphism and antiplatelet effects of clopidogrel in patients undergoing elective coronary stent placement. *Circ Cardiovasc Genet* 2011;**4**:429–36	C
Trenk D, Hochholzer W, Frundi D, Stratz C, Valina CM, Bestehorn HP, *et al.* Impact of cytochrome P450 3A4-metabolized statins on the antiplatelet effect of a 600-mg loading dose clopidogrel and on clinical outcome in patients undergoing elective coronary stent placement. *Thromb Haemost* 2008;**99**:174–81	C
Trenk D, Hochholzer W, Valina CM, Stratz C, Bestehorn H-P, Buettner HJ, *et al.* Clinical events in patients undergoing percutaneous coronary intervention with bare-metal stenting after discontinuation of clopidogrel. *Eur Heart J* 2010;**31**:965	B
Trenk D, Hochholzer W, Valina CM, Stratz C, Bestehorn HP, Buttner HJ, *et al.* Increased incidence of clinical events in patients undergoing percutaneous coronary intervention with baremetal stenting after discontinuation of clopidogrel. *Br J Clin Pharmacol* 2010;**70**:5	B, C
Trenk D, Neumann FJ. Aspirin resistance an underestimated risk in patients with drug-eluting stents? *J Am Coll Cardiol* 2008;**52**:740–2	A
Tschopp TB, Zucker MB. Platelet function tests in disease. *Annu Rev Med* 1973;**24**:1–18	A

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Tsiaousis GZ, Zairis MN, Patsourakos N, Makrygiannis S, Vogiatzidis K, Gougourela E, *et al.* Oral proton pump inhibitors and their impact on the effectiveness of dual anti-platelet therapy during the first year after elective coronary stenting. *J Am Coll Cardiol* 2009;**53**:A335	C
Tsimikas S, Leibundgut G. Post-thienopyridine platelet response, cardiovascular outcomes, and personalized therapy: en attendant Godot. *JACC Cardiovasc Interv* 2010;**3**:657–9	A
Tsui PT, Lau CL, Lo YK, Chan NY, Wu CW, Choy CC, *et al.* Low platelet responsiveness to clopidogrel is related to target lesion revascularization in Chinese. *Am J Cardiol* 2008;**105**(Suppl. 1):25B	C, D
Tsui PT, Lau CL, Lo YK, Mok NS, Lau ST. Effectiveness of clopidogrel in Chinese. *Int J Cardiol* 2011;**147**:S11	B, C
Tsukahara K, Kimura K, Ebina T, Kosuge M, Hibi K, Iwahashi N, *et al.* The relationship between high on-treatment platelet reactivity and rapid angiographic progression of non-culprit coronary lesions in patients with acute coronary syndromes. *J Am Coll Cardiol* 2011;**57**(Suppl. 1):E928	C
Tsukahara K, Kimura K, Morita S, Ebina T, Kosuge M, Hibi K, *et al.* Impact of high-responsiveness to dual antiplatelet therapy on bleeding complications in patients receiving drug-eluting stents. *Circ J* 2010;**74**:679–85	C
Turakhia MP, Murphy SA, Pinto TL, Antman EM, Giugliano RP, Cannon CP, *et al.* Association of platelet count with residual thrombus in the myocardial infarct-related coronary artery among patients treated with fibrinolytic therapy for ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2004;**94**:1406–10	A
Uchiyama S, Yamazaki M, Maruyama S, Handa M, Ikeda Y, Fukuyama M, *et al.* Shear-induced platelet aggregation in cerebral ischemia. *Stroke* 1994;**25**:1547–51	D
Ueno M, Ferreiro JL, Tomasello SD, Tello-Montoliu A, Capodanno D, Seecheran N, *et al.* Impact of pentoxifylline on platelet function profiles in patients with type 2 diabetes mellitus and coronary artery disease on dual antiplatelet therapy with aspirin and clopidogrel. *JACC Cardiovasc Interv* 2011;**4**:905–12	D
Ulehlova J, Slavik L, Krcova V, Galuszka J, Vaclavik J. Platelet gene polymorphisms related to acute myocardial infarction in young patients. *J Thromb Haemost* 2011;**9**:343	D
Undas A, Placzkiewicz-Jankowska E, Zielinski L, Tracz W. Lack of aspirin-induced decrease in thrombin formation in subjects resistant to aspirin. *Thromb Haemost* 2007;**97**:1056–8	D
Valenti R, Migliorini A, Giuliani G, Parodi G, Buonamici P, Cerisano G, *et al.* Nonresponsiveness to clopidogrel and long-term clinical outcome after drug-eluting stenting for unprotected left main coronary disease. *Am J Cardiol* 2009;**104**(Suppl. 1):97D	C
Valenti R, Migliorini A, Parodi G, Marcucci R, Buonamici P, Cerisano G, *et al.* Diabetes mellitus requiring insulin and high residual platelet reactivity after clopidogrel loading dose are predictors of long-term clinical outcome in patients with acute coronary syndrome: the RECLOSE2-ACS diabetes mellitus substudy. *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B114	C
Valenti R, Parodi G, Antoniucci D. High residual platelet reactivity and thrombotic events – reply. *JAMA* 2011;**306**:2561–2	A, B, C
Valenti R, Parodi G, Migliorini A, Marcucci R, Buonamici P, Cerisano G, *et al.* The impact of high residual platelet reactivity after clopidogrel loading on long-term clinical outcome of patients with acute coronary syndromes receiving an invasive treatment: the RECLOSE 2-ACS trial. *J Am Coll Cardiol* 2011;**58**(Suppl. 1):B16	C
Valenti R, Vergara R, Migliorini A, Carrabba N, Cerisano G, Parodi G, *et al.* High residual platelet reactivity after clopidogrel loading and clinical outcome after drug-eluting stenting for chronic total occlusion. *G Ital Cardiol* 2011;**12**(Suppl. 1):36S	C
Valgimigli M, Campo G, Ferrari R, de Cesare N, Meliga E, Vranckx P, *et al.* Response to letter regarding article, 'intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel study'. *Circulation* 2010;**121**:e236	A

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Valles J, Santos MT, Fuset MP, Moscardo A, Ruano M, Perez F, *et al.* Partial inhibition of platelet thromboxane A2 synthesis by aspirin is associated with myonecrosis in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2007;**99**:19–25	D
van Werkum JW, Hackeng CM, Smit J-J, van't Hof AWJ, Verheugt FWA, ten Berg JM. Monitoring antiplatelet therapy with point-of-care platelet function assays: a review of the evidence. *Future Cardiol* 2008;**4**:33–55	A
van Werkum JW, Kleibeuker M, Mieremet N, ten Berg JM, Hackeng CM. Evaluation of the platelet response to clopidogrel with light transmittance aggregometry: peak aggregation or late aggregation? *J Thromb Haemost* 2007;**5**:884–6	C, D
van Werkum JW, ten Berg JM. Platelet reactivity as a risk-factor for stent thrombosis: can this be one of the currently available appropriate methods to determine platelet reactivity? *Eurointervention* 2008;**4**(Suppl. C):11–16	A
van Werkum JW, Topcu Y, Postma S, Kelder JC, Hackeng CM, ten Berg JM, *et al.* Effects of diabetes mellitus on platelet reactivity after dual antiplatelet therapy with aspirin and clopidogrel. *Thromb Haemost* 2008;**99**:637–9	C, D
van Werkum JW, van der Stelt CA, Seesing TH, Hackeng CM, ten Berg JM. A head-to-head comparison between the VerifyNow P2Y12 assay and light transmittance aggregometry for monitoring the individual platelet response to clopidogrel in patients undergoing elective percutaneous coronary intervention. *J Thromb Haemost* 2006;**4**:2516–18	C, D
van Werkum JW, van der Stelt CA, Seesing TH, ten Berg JM, Hackeng CM. The flow cytometric VASP assay can be used to determine the effectiveness of clopidogrel in patients treated with abciximab. *J Thromb Haemost* 2007;**5**:881–3	C, D
Varanasi JS, Steinhubl SR. Antiplatelet effect of aspirin in patients with cerebrovascular disease. *Stroke* 2004;**35**:e144–5	A
Vatakencherry A, Narang J, Kim J, Wasnick J, Langer D, Bennett H. Aspirin resistance in neurosurgical vascular bypass procedures. *J Neurosurg Anesthesiol* 2008;**20**:294–5	D
Verschuren JJ, Boden H, Wessels JA, Guchelaar H-J, Schalij MJ, Jukema JW. Platelet pharmacogenetics in common clinical practice. *Circulation* 2011;**124**(Suppl. 1):A12668	C
Vila PM, Zafar MU, Badimon JJ. Platelet reactivity and nonresponse to dual antiplatelet therapy: a review. *Platelets* 2009;**20**:531–8	A
Violi F, Pignatelli P, Basili S. Letter by Violi *et al.* regarding article, 'Association of cyclooxygenase-1-dependent and -independent platelet function assays with adverse clinical outcomes in aspirin-treated patients presenting for cardiac catheterization'. *Circulation* 2010;**122**:e429	A
Violi F, Pignatelli P. Aspirin resistance. *Lancet* 2006;**367**:2059–60	A
Violi F, Pignatelli P. The need for a consistent definition of 'aspirin resistance'. *J Thromb Haemost* 2006;**4**:1618–19	A
Vlachojannis GJ, Dimitropoulos G, Alexopoulos D. Clopidogrel resistance: current aspects and future directions. *Hell J Cardiol* 2011;**52**:236–45	A
Volenti R, Vergara R, Migliorini A, Carrabba N, Cerisano G, Parodi G, *et al.* High residual platelet reactivity after clopidogrel loading and clinical outcome after drug-eluting stenting for chronic total occlusion. *J Am Coll Cardiol* 2010;**56**(Suppl. 1):B49	C
von Kaulla E, von Kaulla KN. [Detection of a thrombotic tendency by means of coagulation tests (author's transl).] *MMW Munch Med Wochenschr* 1974;**116**:1387–96	A
von Pape KW, Strupp G, Bonzel T, Bohner J. Effect of compliance and dosage adaptation of long term aspirin on platelet function with PFA-100 in patients after myocardial infarction. *Thromb Haemost* 2005;**94**:889–91	D
Von Pape KW, Dzijan-Horn M, Bohner J, Spannagl M, Weisser H, Calatzis A. Control of aspirin effect in chronic cardiovascular patients using two whole blood platelet function assays: PFA-100 and Multiplate. *Hamostaseologie* 2007;**27**:155–60	D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Voora D, Horton J, Shah SH, Shaw LK, Newby LK. Polymorphisms associated with in vitro aspirin resistance are not associated with clinical outcomes in patients with coronary artery disease who report regular aspirin use. *Am Heart J* 2011;**162**:166–72	C
Waheed R, Lockhart MK, Gopinath D, Mohammed A, Wazir S, Quealy K, *et al.* Prevalence of aspirin resistance in patients with peripheral arterial disease. *Vasc Med* 2010;**15**:143–4	D
Walters TK, Mitchell DC, Wood RF. Low-dose aspirin fails to inhibit increased platelet reactivity in patients with peripheral vascular disease. *Br J Surg* 1993;**80**:1266–8	D
Wang B. Progress of aspirin resistance. *Chin J Cerebrovasc Dis* 2010;**7**:553–6	A
Wang L, Wang X, Chen F. Clopidogrel resistance is associated with long-term thrombotic events in patients implanted with drug-eluting stents. *Drugs R D* 2010;**10**:219–24	C
Wang TY, Ou FS, Roe MT, Harrington RA, Ohman EM, Gibler WB, *et al.* Incidence and prognostic significance of thrombocytopenia developed during acute coronary syndrome in contemporary clinical practice. *Circulation* 2009;**119**:2454–62	C
Wang X-D, Zhang D-F, Liu X-B, Lai Y, Qi W-G, Luo Y, *et al.* Modified clopidogrel loading dose according to platelet reactivity monitoring in patients carrying ABCB1 variant alleles in patients with clopidogrel resistance. *Eur J Intern Med* 2012;**23**:48–53	C
Wang XD, Zhang DF, Zhuang SW, Lai Y. Modifying clopidogrel maintenance doses according to vasodilator-stimulated phosphoprotein phosphorylation index improves clinical outcome in patients with clopidogrel resistance. *Clin Cardiol* 2011;**34**:332–8	C
Wang ZJ, Zhou YJ, Liu YY, Yu M, Shi DM, Zhao YX, *et al.* Impact of clopidogrel resistance on thrombotic events after percutaneous coronary intervention with drug-eluting stent. *Thromb Res* 2009;**124**:46–51	C
Warner TD, Mitchell JA, Kirkby NS. Short thromboelastography and the identification of high platelet reactivity while on and off therapy. *Heart* 2012;**98**:679–80	A
Wasowicz M, McCluskey SA, Wijeysundera DN, Yau TM, Meinri M, Beattie WS, *et al.* The incremental value of thrombelastography for prediction of excessive blood loss after cardiac surgery: an observational study. *Anesth Analg* 2010;**111**:331–8	C
Weber AA, Zimmermann KC, Meyer-Kirchrath J, Schror K. Cyclooxygenase-2 in human platelets as a possible factor in aspirin resistance. *Lancet* 1999;**353**:900	A
Weber ZA, Rodgers PT. The clinical significance of the interaction between proton pump inhibitors and clopidogrel. *J Pharm Technol* 2010;**26**:22–6	B, C
Welsby IJ, Jiao K, Ortel TL, Brudney CS, Roche AM, nett-Guerrero E, *et al.* The kaolin-a. *J Cardiothorac Vasc Anesth* 2006;**20**:531–5	C, D
Wenaweser P, Hess O. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol* 2005;**46**:CS5–6	D
Wientong P, Jongjarornprasert W, Panomvana D. Platelet aggregation and serum thromboxane B2 level after taking 60 mg/day of aspirin in type 2 diabetic Thai patients. *Int J Pharm Pharm Sci* 2011;**3**(Suppl. 3):47–50	D
Willoughby SR, Stewart S, Holmes AS, Chirkov YY, Horowitz JD. Platelet nitric oxide responsiveness: a novel prognostic marker in acute coronary syndromes. *Arterioscler Thromb Vasc Biol* 2005;**25**:2661–6	C
Winckers K, Poenitz V, van Oerle R, Noordermeer K, Ten CH, Nilsen DWT. A case control study on platelet response to antiplatelet therapy in survivors of late stent thrombosis. *J Thromb Haemost* 2009;**7**(S2):649	D
Windelov NA, Welling KL, Ostrowski SR, Johansson PI. The prognostic value of thrombelastography in identifying neurosurgical patients with worse prognosis. *Blood Coagul Fibrinolysis* 2011;**22**:416–19	B, C
Wong S, Appleberg M, Lewis DR. Antiplatelet therapy in peripheral occlusive arterial disease. *ANZ J Surg* 2006;**76**:364–72	C
Wong S, Appleberg M, Ward CM, Lewis DR. Review finds further work is required to define and assess the incidence of aspirin resistance. *Evid Based Cardiovasc Med* 2004;**8**:267	A

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TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Wong S, Morel-Kopp MC, Chen Q, Appleberg M, Ward CM, Lewis DR. Overcoming aspirin resistance: increased platelet inhibition with combination aspirin and clopidogrel and high dose aspirin therapy in aspirin resistant patients with peripheral vascular disease. *Thromb Haemost* 2006;**95**:1042–3	D
Woo JS, Kim W, Lee JH, Choi E-Y, Jang WS, Kim GS. Association of platelet reactivity and endothelial function and anti-inflammatory effects in patients with stable coronary artery disease. *Am J Cardiol* 2012;**109**(Suppl. 1):77S	C, D
Woo KS, Kim BR, Kim JE, Goh RY, Yu LH, Kim MH, *et al.* Determination of the prevalence of aspirin and clopidogrel resistances in patients with coronary artery disease by using various platelet-function tests. *Kor J Lab Med* 2010;**30**:460–8	D
Worrall A, Armesilla A, Norell M, Khogali S, Cusack M, Smallwood A, *et al.* The presence of the CYP p450 C19*2 allele is associated with impaired response to clopidogrel as measured by the verifynow P2Y12 near-patient testing device in patients undergoing coronary angiography. *Eur Heart J* 2009;**30**:327	C
Wurtz M, Grove EL, Wulff LN, Kaltoft AK, Tilsted HH, Jensen LO, *et al.* Patients with previous definite stent thrombosis have a reduced antiplatelet effect of aspirin and a larger fraction of immature platelets. *JACC Cardiovasc Interv* 2010;**3**:828–35	D
Xanthopoulou I, Tsigkas G, Damelou A, Theodoropoulos KC, Kassimis G, Chouchoulis K, *et al.* Predictors of high on-treatment platelet reactivity early after clopidogrel loading in ST elevation myocardial infarction patients. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E485	B
Xu Z-H, Jiao J-R, Yang R, Luo B-Y, Wang X-F, Wu F. Aspirin resistance: clinical significance and genetic polymorphism. *J Int Med Res* 2012;**40**:282–92	B
Yahia AM, Latorre J, Gordon V, Whapham J, Malek A, Fessler RD. Thromboembolic events associated with Neuroform stent in endovascular treatment of intracranial aneurysms. *J Neuroimaging* 2010;**20**:113–17	C
Yamaguchi Y, Abe T, Sato Y, Moriki T, Murata M. Point-of-care assessment after clopidogrel treatment predicts clinical outcomes of patients with cardiovascular disease: a meta-analysis of six studies. *J Thromb Haemost* 2011;**9**:544	C
Yamane K, Ikeda T, Taniguchi R, Kita T, Kimura T, Horiuchi H. Characterization of the antiplatelet effect of aspirin at enrollment and after a 2-year follow-up in the real clinical setting in Japan. *J Thromb Haemost* 2011;**9**:85	D
Yilmaz MB, Balbay Y, Caldir V, Ayaz S, Guray Y, Guray U, *et al.* Late saphenous vein graft occlusion in patients with coronary bypass: possible role of aspirin resistance. *Thromb Res* 2005;**115**:25–9	D
Yong G, Rankin J, Ferguson L, Thom J, French J, Brieger D, *et al.* Randomized trial comparing 600- with 300-mg loading dose of clopidogrel in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: results of the Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial. *Am Heart J* 2009;**157**:60–9	C
Yoo JR, Kim SY, Kim KS, Joo S-J. Prevalence and clinical characteristics of aspirin resistance defined by impedance platelet aggregometry. *Am J Cardiol* 2012;**109**(Suppl. 1):13S	D
Zalewski J, Lech P, Durak M, Roslawiecka A, Gajos G, Undas A, *et al.* Platelet function in patients with ST-segment elevation myocardial infarction is associated with microvascular injury. *Eur Heart J* 2010;**31**:772	D
Zawilska KM, Jamrozek-Jedlinska M, Duszynska M, Jedlinski I, Slomczynski M. Time-related changes of the sensitivity to anti-platelet therapy in patients with acute coronary syndrome after percutaneous coronary intervention. *J Thromb Haemost* 2011;**9**:547–8	D
Zhao YJ, Zhou LJ, Li WM, Liu PD, Chen YD, Song LY. [Safety and efficacy of firebird drug-eluting stent combination tirofiban in patients with acute coronary syndrome.] *Zhonghua Yi Xue Za Zhi* 2008;**88**:2553–5	C
Zhivoderov VM, Kondratchik SI. [Relation between disorders of lipid metabolism and the process of blood coagulation in myocardial infarct according to thrombelastographic data.] *Ter Arkh* 1975;**47**:68–72	D
Zimmermann N, Kienzle P, Weber AA, Winter J, Gams E, Schror K, *et al.* Aspirin resistance after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2001;**121**:982–4	D

TABLE 85 List of excluded articles with reason (*continued*)

Article	Reason for exclusion
Zimmermann N, Kurt M, Winter J, Gams E, Wenzel F, Hohlfeld T. Detection and duration of aspirin resistance after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2008;**135**:947–8	D
Zoller H, Suss W, Gross W. [Thrombocytes, blood coagulation factors and fibrinolysis following aortocoronary venous bypass operation.] *Vasa Suppl* 1991;**32**:305–8	D
Zurn CS, Geisler T, Paterok M, Gawaz M. [Influence of statins on the antiplatelet effect of clopidogrel and on cardiovascular outcome in patients after coronary intervention.] *Dtsch Med Wochenschr* 2008;**133**:817–22	C
Zytkiewicz M, Gielwanowska L, Wojtasinska E, Psuja P, Zawilska K. Resistance to acetylsalicylic acid in patients after ischemic stroke. *Pol Arch Med Wewn* 2008;**118**:727–33	D

A, study; B, population; C, PFT; D, outcome.

TABLE 86 Studies with insufficient information to make a selection decision

Reference	Characteristic requiring further information
Chen WH, Lee PY, Ng W, Kwok JY, Cheng X, Lee SW, *et al.* Relation of aspirin resistance to coronary flow reserve in patients undergoing elective percutaneous coronary intervention. *Am J Cardiol* 2005;**96**:760–3	D
Cho K-H, Kim J-H, Sohn S-I. The clinical significance of aspirin resistance in aspirin-taking patients with acute ischemic stroke. *Int J Stroke* 2010;**5**:311–12	C
Geisler T, Mueller K, Aichele S, Stellos K, Zuern CS, Htun P, *et al.* Impact of inflammatory markers on platelet function and cardiovascular outcome in patients with symptomatic coronary artery disease. *Eur Heart J* 2010;**31**:156–7	D
Horiuchi H, Yokoi H, Kimura T, Isshiki T, Ogawa H, Ikeda Y. More rapid and greater pharmacodynamic effects of prasugrel in Japanese patients with stable coronary artery disease (CAD) undergoing elective PCI. *J Thromb Haemost* 2011;**9**:86	C
Jin L, Xu SH, Yan XW. [The effect of low dose aspirin on the platelet function in patients with acute myocardial infarction.] *Chung-Hua Nei Ko Tsa Chih* 1993;**32**:542–4	D
Kojuri J, Mahmoody Y, Sabegh BZ, Jannati M, Mahboodi A, Khalili A. Dose-related effect of aspirin on laboratory-defined platelet aggregation and clinical outcome after coronary stenting. *Cardiovasc Ther* 2010;**28**:147–52	C
Liu F, Liu J-C, Wang D-M, Li J, Wang L-J, Liu Y. Aspirin and clopidogrel resistance in patients with symptomatic carotid and vertebrobasilar artery stenosis. *Chin J Cerebrovasc Dis* 2008;**5**:15	D
Meves SH, Overbeck U, Endres HG, Krogias C, Neubauer H. Dose-dependent effect of early antiplatelet therapy in acute ischaemic stroke. *Thromb Haemost* 2012;**107**:69–79	D
Morofuji Y, So G, Hiu T, Kawakubo J, Hayashi K, Kitagawa N, *et al.* Preoperative analysis of platelet aggregability in carotid surgery. *Neurol Surg* 2011;**39**:459–63	D
Sezer O, Stepper W, Schneider T, Welp H, Tjan TD, Sauerland C, *et al.* Residual platelet activity in LVAD patients with stroke. *Thorac Cardiovasc Surg* 2011;**59**:V57	C
Valgimigli M. Main results of the tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel study (3T/2R). *Clin Res Cardiol* 2008;**97**:853–4	C
Zhang Y, Liang J, Zhou YJ, Yuan H, Zhang YZ, Dong L. [Study on the relationship between aspirin resistance and incidence of myonecrosis after non-emergent percutaneous coronary intervention.] *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih* 2005;**33**:695–9	D

C, PFT; D, outcome.

Appendix 7 Prognostic/diagnostic utility systematic review: articles in which outcome data are not presented in relation to platelet function test results

Below is a list of 62 articles that met the inclusion criteria for review and contained PFT results and clinical outcome data but failed to report the outcome data in relation to the test result. These articles provided no relevant information on prognostic utility of the PFT but indicate that there may be unreported relevant data.

Abumiya T, Houkin K, Morita S, Fukuhara S. Prospective study of platelet aggregation in antiplatelet therapy. *Stroke* 2009;**40**:e248.

Al-Atassi T, Lapierre H, Boodhwani M, Lam K, Forgie M, Rubens F, *et al.* Cerebral microembolization after bioprosthetic aortic valve replacement: an open-label study of daily warfarin + aspirin versus aspirin alone. *Circulation* 2011;**124**(Suppl.1):A14512.

Althoff TF, Fischer M, Langer E, Ziemer S, Baumann G. Sustained enhancement of residual platelet reactivity after coronary stenting in patients with myocardial infarction compared to elective patients. *Thromb Res* 2010;**125**:e190–6.

Altman R, Rivas AJ, Gonzalez CD. Bleeding tendency in dual antiplatelet therapy with aspirin/clopidogrel: Rescue of the template bleeding time in a single-center prospective study. *Thromb J* 2012;**10**:3.

Ashbrook M, Schwartz J, Heroux A, Walenga J, Jeske W, Escalante V, *et al.* Left ventricular assist device induced coagulation and platelet activation and effect of the current anticoagulant therapy regimen. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E880.

Atiemo AD, Ng'Alla LS, Vaidya D, Williams MS. Abnormal PFA-100 closure time is associated with increased platelet aggregation in patients presenting with chest pain. *J Thromb Thrombolysis* 2008;**25**:173–8.

Beigel R, Hod H, Fefer P, Asher E, Novikov I, Shenkman B, *et al.* Relation of aspirin failure to clinical outcome and to platelet response to aspirin in patients with acute myocardial infarction. *Am J Cardiol* 2011;**107**:339–42.

Beigel RS, Hod H, Shenkman B, Fefer P, Savion N, Varon D, *et al.* Aspirin failure is associated with worse clinical outcome but not with an inadequate platelet response to aspirin in patients with acute myocardial infarction. *J Am Coll Cardiol* 2010;**55**(Suppl. 1):A108.

Berent R, Auer J, Franklin B, Schmid P, von Duvillard SP. Platelet response to aspirin 50 and 100 mg in patients with coronary heart disease over a five-year period. *Am J Cardiol* 2011;**108**:644–50.

Berrouschot J, Schwetlick B, von Twickel G, Fischer C, Uhlemann H, Siegemund T, *et al.* Aspirin resistance in secondary stroke prevention. *Acta Neurol Scand* 2006;**113**:31–5.

Blanchard O, Ehrensperger E, Minuk J, Solymoss S. Antiplatelet resistance in patients with recent cerebral ischemic events. *Stroke* 2011;**42**:e346.

Bobescu E, Radoi M, Dobreanu D, Rogozea L, Doka B, Catanescu G. Drugs with effects in reduction of oxidative stress, platelets hyperactivity, hypercoagulability status and incidence of sudden death in ACS. *Fundam Clin Pharmacol* 2011;**25**:I.

Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Hackeng CM, ten Berg JM. Dual antiplatelet therapy resistance to aspirin and clopidogrel identifies patients at the highest risk of recurrent atherothrombotic events after percutaneous coronary intervention. *Circulation* 2010;**122**:A16601.

Catella-Lawson F, Kapoor S, Moretti D, De Marco S, Vigilante GJ, Cucchiara AJ, *et al.* Oral glycoprotein IIb/IIIa antagonism in patients with coronary artery disease. *Am J Cardiol* 2001;**88**:236–42.

Christie DJ, Kottke-Marchant K, Gorman RT. Hypersensitivity of platelets to adenosine diphosphate in patients with stable cardiovascular disease predicts major adverse events despite antiplatelet therapy. *Platelets* 2008;**19**:104–10.

Claeys MJ, Van der Planken MG, Michiels JJ, Vertessen F, Dilling D, Bosmans JM, *et al.* Comparison of antiplatelet effect of loading dose of clopidogrel versus abciximab during coronary intervention. *Blood Coagul Fibrinolysis* 2002;**13**:283–8.

Collet J-P, Pena A, Hulot JS, Silvain J, Barthelemy O, Beygui F, *et al.* Can we override clopidogrel resistance? *Eur Heart J* 2009;**30**:199.

Cuisset T, Frere C, Quilici J, Bali L, Poyet R, Morange PE, *et al.* Predictive value of post treatment platelet reactivity for occurrence of post-discharge bleeding after non ST elevation acute coronary syndrome. *Arch Cardiovasc Dis Suppl* 2010;**2**:1.

Djukanovic N, Todorovic Z, Obradovic S, Zamaklar-Trifunovic D, Njegomirovic S, Milic NM, *et al.* Abrupt cessation of one-year clopidogrel treatment is not associated with thrombotic events. *J Pharmacol Sci* 2011;**117**:12–18.

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